MAY 20 1932

Vol. III MAY, 1932 No. 4

Medical Lib

THE JOURNAL OF ALLERGY

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PUBLISHED BI-MONTHLY

OFFICIAL ORGAN OF
THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE ASSOCIATION FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD,
ST. LOUIS, U. S. A.

Entered as Second Class Matter at Post Office at St. Louis, Mo.
Additional Entry at Fulton, Mo.

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The Journal of Allergy

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The Journal of Allergy

VOL. III MAY, 1932 No. 4

Original Articles

A STUDY OF THE CALCIUM, PHOSPHORUS AND POTASSIUM OF THE SERUM AND SPINAL FLUID IN ASTHMA*

D. M. LIERLE, M.D., AND R. A. SAGE, B.A.
IOWA CITY, IOWA

THE content of calcium and potassium in the serum of asthmatic patients has been the subject of considerable study in recent years. Kylin[2] was probably the first to call attention to abnormally high potassium values in such patients. Cantarow[4] and Novak and Hollender[5] found diminished calcium values. Klauder and Brown,[8] Briggs,[6] Brems[7] and Unshelm[9] have reported calcium figures generally accepted as normal. The average potassium values reported by these authors do not approach the high average found by Kylin.[2] The present study is concerned with calcium, phosphorus and potassium in both serum and spinal fluid in 20 patients with bronchial asthma.

The method used for the estimation of potassium by practically all of the investigators quoted in Tables V and VI is the Kramer-Tisdall technic or some modification of it. This method has been critized by Kerr,[15] who found that "the sodium cobalti-nitrite reagent precipitated something in serum, probably a protein, which occluded part of the reagent," and thus led to variable results. Shohl and Bennett[16] believe that the precipitate of potassium cobalti-nitrite, obtained by the Kramer-Tisdall technic, is not of constant composition. These disadvantages may account for many of the extremely wide variations found in the literature. The Kramer-Tisdall method, however, has advantages in clinical use, since it consumes less time and is less expensive than many of the other methods. The potassium values reported by us on both serum and spinal fluid were determined by the Kramer-Tisdall method. The original procedure[11] was modified by removing the slight scum of protein which collects around the edge of the surface of the liquid. This scum was removed with a cotton swab after the potassium precipitate had been thoroughly centrifuged. The 0.01 normal sodium oxalate originally described was replaced by 0.02 normal solution. Blood and spinal fluid were drawn simultaneously usually within two or three hours after meals. Hemolyzed samples were discarded. The serum was separated

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from the clot within an hour, and the potassium determinations were carried out within twenty-four hours. Calcium was determined by the method described by Kramer and Tisdall.[17] Phosphorus was determined on the calcium filtrate of both blood and spinal fluid by the method of Gunther and Greenberg.[18] Serum protein was determined by the micro-Kjeldahl method.[1]

TABLE I

SERUM CALCIUM AND POTASSIUM, AND POTASSIUM CALCIUM RATIOS IN ASTHMA

NAME	SEX	AGE	(MG. PER 100 C.C.) CA	K	K/CA
K. M.	F.	44	10.3	20.2	1.96
E. F.	F.	34	10.3	26.8	2.60
S. R.	M.	42	9.7	20.4	2.10
O. T.	F.	56	11.2	15.0	1.34
G. F.	F.	42	10.0	15.0	1.50
E. W.	F.	66	10.4	16.0	1.54
R. H.	F.	22	10.6	19.7	1.86
L. H.	M.	56	11.3	18.0	1.59
G. H.	F.	25	11.4	17.4	1.53
F. C.	F.	7	10.3	17.6	1.71
N. McC.	F.	41	10.7	19.4	1.81
R. V. D.	M.	6	10.3	20.6	2.00
I. M.	F.	18	10.9	18.0	1.65
A. W.	M.	5	10.1	18.6	1.84
M. E.	F.	8	11.1	20.4	1.84
C. W.	M.	21	10.7	18.8	1.76
F. L.	F.	23	11.8	16.8	1.42
L. C.	M.	15	10.7	23.1	2.16
R. C.	M.	13	10.7	16.2	1.51
E. Q.	M.	49	10.5	21.9	2.08
Averages			10.65	19.0	1.79

TABLE II

SPINAL FLUID CALCIUM, POTASSIUM, AND POTASSIUM CALCIUM RATIOS; AND RATIOS OF SERUM CALCIUM—SPINAL FLUID CALCIUM AND SERUM POTASSIUM—SPINAL FLUID POTASSIUM IN ASTHMA

NAME	(MG. PER 100 C.C.) CA	K	RATIO K/CA	CA SERUM / CA SPINAL FLUID	K SERUM / K SPINAL FLUID
K. M.	4.7	...	...	2.08	...
K. M.	4.6	...	...	2.26	...
E. F.	4.7	9.7	2.07	2.19	2.75
S. R.	5.0	10.4	2.10	1.95	1.96
O. T.	5.4	9.9	1.83	2.07	1.51
E. W.	4.8	11.4	2.38	2.17	1.40
R. H.	4.8	11.8	2.47	2.28	1.66
L. H.	5.6	11.4	2.03	2.01	1.57
G. H.	4.6	11.0	2.39	2.48	1.58
N. McC.	4.8	10.6	2.20	2.22	1.83
E. M.	5.2	12.1	2.32	2.09	1.48
H. W.	4.8	10.9	2.27	2.10	1.71
M. E.	5.2	9.5	1.82	2.13	2.14
F. L.	5.1	10.1	1.98	2.31	1.66
L. C.	4.8	10.9	2.27	2.22	2.11
R. C.	4.7	10.7	2.27	2.27	1.51
Averages	4.93	10.74	2.17	2.18	1.78

Twenty patients with bronchial asthma are reported in the present study, Tables I, II, and III. The average value for calcium is 10.65 mg., for potassium, 19.0 mg. These averages fall within the limits accepted as normal by Hawk and Bergeim.[1] Seven control patients showed an average calcium of 10.7 mg., and an average potassium of 20.3 mg. The variation in potassium in asthma agrees with that reported by Peterson and Levinson[14] for 100 non-asthmatic patients, except that two of our

TABLE III

CALCIUM, PHOSPHORUS, AND CALCIUM PHOSPHORUS RATIOS IN SERUM AND SPINAL FLUID IN ASTHMA

(MG. PER 100 C.C.)

	BLOOD SERUM				SPINAL FLUID		
NAME	CA	P	RATIO CA/P	(GM. PER 100 C.C.) SERUM PROTEIN	CA	P	RATIO CA/P
K. M.	9.8	3.2	3.06	7.9	4.7	1.2	3.92
K. M.	10.3	3.6	2.86	8.5	4.6	1.5	3.09
E. F.	10.3	3.4	3.02	8.1	4.7	2.6	3.73
S. R.	9.7	3.8	2.54	8.0	5.00	1.2	4.20
O. T.	11.2	3.5	3.20	8.4	5.4	1.6	3.37
G. F.	10.0	3.6	2.78	7.2	..	..	...
E. W.	10.4	3.2	3.22	7.5	4.8	1.4	3.43
R. H.	10.6	3.1	3.41	6.8	4.8	1.5	3.20
L. H.	11.3	3.7	3.06	7.6	5.6	1.5	3.73
G. H.	11.4	3.2	3.56	8.7	4.6	1.9	2.42
F. C.	10.3	2.4	4.30	6.0	..	..	...
N. McC.	10.7	2.7	3.98	8.7	4.8	2.3	2.08
R. V. D.	10.3	3.6	2.86	6.9	4.9	2.50	1.96
I. M.	10.9	3.6	3.02	8.2	5.2	1.50	3.47
A. W.	10.1	5.1	1.98	7.4	4.8	1.4	3.43
M. E.	11.1	4.8	2.30	8.3	5.2	1.6	3.25
C. W.	10.7	3.2	3.34	7.7	..	..	...
F. L.	11.8	3.0	3.94	8.9	5.1	1.20	4.25
L. C.	10.7	5.2	2.03	7.7	4.8	1.60	3.0
R. C.	10.7	4.9	2.19	7.7	4.7	1.60	2.94
Averages	10.62	3.64	3.03	7.8	4.92	1.65	3.26

TABLE IV

SERUM CALCIUM, POTASSIUM, AND POTASSIUM CALCIUM RATIOS IN NON-ASTHMATIC CONDITIONS

NAME	DIAGNOSIS	MG. PER 100 C.C. CA	K	RATIO K/CA
Mrs. F.	Osteoporosis	10.0	20.1	2.01
K. G.	Myasthenia endocrine imbalance	11.0	22.9	2.08
Mrs. S.	Osteoporosis vertebrae	10.8	22.1	...
Mrs. S.	Osteoporosis vertebrae	...	21.7	...
Mrs. S.	Osteoporosis vertebrae	...	22.4	2.03
L. B.	Diabetes	10.8	21.4	1.98
T. L.	Paget's disease	10.2	16.8	1.64
D. H.	Vasomotor rhinitis	11.1	16.8	1.51
H. D.	Cystitis	11.0	18.2	1.65
		10.70	20.26	1.84

patients showed values of 15 mg. each. The potassium calcium ratio approximates that offered as normal by Briggs[6] and by Brems,[7] and falls within the limits of those reported by Peterson and Levinson.[14] Our potassium values do not check with those of Kylin.[2, 3] Calcium, phosphorus and protein of the serum were within normal limits, and are listed in Table III. Our control data, listed in Table IV, were all well within normal limits.

In order to compare the work of various authors, their results are summarized in Table V. Averages from our own series of 20 patients with asthma are also included. The normal and the control values of several investigators are shown in Table VI together with our own control data. Considerable variation in the potassium range is observed, although the average figures show but slight variation.

TABLE V

SERUM CALCIUM, POTASSIUM, AND POTASSIUM CALCIUM RATIOS IN ASTHMA

AUTHOR	NO. OF PATIENTS	AV. CA (MG. PER 100 C.C.)	AV. K (MG. PER 100 C.C.)	RANGE K (MG. PER 100 C.C.)	AV. K/CA	RANGE K/CA	REMARKS
Kylin[2]	21	11.09	25.8	20.9-31.2	2.33	1.64-2.93	
Kylin[3]	19	10.6	26.01	23. -30.5	2.47	2.04-2.93	
Cantarow[4]	25	7.00-12.6					
Novak-Hollender[5]	12	9.4 8.7-10.5					
Briggs[6]	2	10.3	18.2	17.5-18.8	1.79	1.52-2.06	Plasma
Brems[7]	20	11.21 10.3-12.5	20.19	16.6-25.8	1.80	1.42-2.51	
Klauder-Brown[8]	4	9.6	20.7	18.8-24.8	2.16	1.84-2.41	Asthma with prurigo Besnier
Unshelm[9]	17	11.1	21.86	19.5-26.1	1.98	1.77-2.35	
Authors' data	20	10.65	19.0	15.0-26.8	1.79	1.51-2.60	

Calcium, phosphorus and potassium were also determined on spinal fluid drawn simultaneously with blood. The results are found in Tables II and III. These results agree with generally accepted normal values, although the figures for potassium are somewhat lower than those reported by Eisler,[22] and by Pincus and Kramer.[13] On the other hand, Kral, Stary and Winteritz[23] have reported potassium analyses which agree closely with our own. Merritt and Bauer[19] have pointed out the striking constancy of calcium in spinal fluid, an observation which is confirmed by our group. Four spinal fluids used as controls were taken at random from the neurologic service. The fluids had been kept in the ice box for several days. The average potassium was 12.8 mg. Other samples with traces of turbidity were analyzed and the results were invariably high. None of the spinal fluids from our group of asthmatics

TABLE VI

SERUM CALCIUM AND POTASSIUM, AND POTASSIUM-CALCIUM RATIOS IN NON-ASTHMATIC CONDITIONS

AUTHOR	NO. OF PATIENTS	AV. CA (MG. PER 100 C.C.)	AV. K (MG. PER 100 C.C.)	RANGE K (MG. PER 100 C.C.)	AV. K/CA RATIOS	RANGE K/CA RATIOS	REMARKS
Hawk-Bergeim[1]		9-11		16. -22.			
Kylin[3]	19	10.6	20.7	18. -24.	1.98		Kramer-Tisdall method
Briggs[6]	40	9.6	19.60	14.9-24.5			Plasma—various pathologic cases Blood: nonnephritic
Brems[7]	21	11.48	17.97	15.5-23.4	1.62	1.17-2.24	Kramer-Tisdall method
Klauder-Brown[8]	8			19.1-24.0		1.72-2.08	Kramer-Tisdall method
Unshelm[9]	9	11.5	20.5	19.9-21.8	1.78	1.69-1.91	
Jacobs-Hoffman[10]	10 10		19.02 20.5	16.6-20.7 18.4-21.9			Kramer-Tisdall method Jacobs-Hoffman method
Kramer-Tisdall[11]	13		19.5				
Kramer-Tisdall[12]	10 16		19.6 19.8	19. -20. 17.9-21.3			Direct determination After ashing
Pincus-Kramer[13]	3	10.5	21.7	20.0-24.2	2.06	1.90-2.28	
Peterson-Levinson[14]	100 20	10.17	20.4	13.4-28.8 16.6-27.4	2.00	1.12-3.20 1.7 -2.4	100 controls clinical blood Absolutely normal (method of Kerr)
Wilkins-Kramer[24]			18-22	17.7-26.3			
Authors' data	7	10.70	20.26	16.8-22.9	1.84	1.51-2.08	

showed turbidity, and the determinations were made within twenty-four hours after the fluid was drawn. The results of several investigators reporting spinal fluid analyses are summarized in Table VII.

Our averages of sixteen asthmatic patients are included for purposes of comparison. All of the other data in Table VII are compiled from patients with non-asthmatic disorders. The averages on calcium and phosphorus are surprisingly close, while those reported on spinal fluid potassium show somewhat wider variation.

SUMMARY AND CONCLUSIONS

1. Determinations of calcium, phosphorus, potassium and protein were made on the serum of twenty patients; and calcium, phosphorus and potassium on sixteen patients, all with asthma.

TABLE VII

CALCIUM, PHOSPHORUS AND POTASSIUM OF SPINAL FLUID IN ASTHMA

AUTHOR	NO. OF PATIENTS	AVERAGE CA	AVERAGE P	AVERAGE K	REMARKS
Cantarow[4]	172	4.5-5.5 (4.0-7.75)			
Pincus-Kramer[13]	3	4.8 (4.4-5.0)	1.23 (0.8-1.8)	15.1 (12.8-16.6)	Normal
	10	4.95 (4.6-5.4)	1.38 (1.0-1.8)	14.7 (12.0-17.4)	Various diseases
Merritt-Bauer[19]	49	5.00 (4.5-5.23)			Non-suppurative central nervous disease
	8		1.53		
Wilcox, Lyttle, Hearn[20]	18	5.2 (4.0-6.3)	1.7 (1.2-2.1)		
Fremont-Smith[21]	20	4.8 (4.1-5.9)	1.5 (1.2-2.0)		Phosphorus determined in 9
Eisler[22]	19	5.2 (4.92-5.64)		12.98-13.47	
Kral, Stary, Winteritz[23]	43			11.7 (5.3-15.6)	
Authors' data	16	4.93 (4.6-5.6)	1.65 (1.2-2.6)	10.74 (9.5-11.8)	Asthma
	4			12.8	Controls

2. Tables are given including summaries of the work of other investigators together with our own data.

3. Values found in serum did not show marked difference from generally accepted normal values, nor great variation from averages of control groups.

4. Calcium, phosphorus and potassium data on spinal fluid showed no striking departure from normal values, and agree well with those of other investigators.

5. Our values for serum potassium in asthma do not check with those reported by Kylin,[2, 3] but compare with those reported by Brems[7] and by Unshelm.[9]

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RECENT OBSERVATIONS IN THE STUDY OF ASTHMA DUE TO FOOD ALLERGY*

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In 1929 Osman[1] of England recommended a generous use of sugar and sweets, particularly in the form of dextrose (glucose) in the treatment of asthma in children. On the other hand, the following year (1930) Peshkin and Fineman[2] reported favorable results with a ketogenic and relatively low carbohydrate high fat diet in a series of chronic asthmatic children. With these reports in mind, it was thought that it would be of great interest to observe under more or less controlled conditions the response of a given case of chronic asthma to the high carbohydrate diet and to the low carbohydrate diet.

For these observations a girl, twelve years of age, was selected and admitted to the University Hospital. She gave a history of asthmatic attacks since the age of four years, before which she had been chiefly troubled with eczema. The asthmatic attacks were primarily caused in this patient by certain foods. Fish, especially codfish, eggs, peas and nuts produced the most marked reactions.

The family history of the patient revealed the fact that the father has slight asthmatic attacks, and the mother has a dry scaly skin. Three sisters are in good health and have no eczema or asthma. Two brothers, on the other hand, are troubled with eczema.

Upon admission to the hospital the patient was thoroughly examined and found to be a well-developed and well-nourished white female child. Her weight was 42.9 kilo. The skin showed some eczema, most marked on the exposed parts of the body. There were a few cavities in the teeth. The tonsils were completely removed. An x-ray examination of the sinuses revealed the right maxillary sinus slightly smaller than normal with slight thickening of the mucous membrane. The remaining sinuses were normal.

The chest was carefully examined. It appeared to be slightly barrel shaped. Percussion did not yield any degree of emphysema. Auscultation showed that the patient was having a mild asthmatic attack, for there were present especially over the lower portion of the chest the typical asthmatic, wheezing respiratory sounds with occasionally a few râles on the right side.

Urine examinations were negative, and complete blood studies were negative except that on several occasions the eosinophile count was slightly higher than the average figure. Blood chemical studies were negative. The Wassermann tests were negative. A gastric analysis

*From the Department of Pediatrics of the University of Minnesota.

showed no free hydrochloric acid, and a total acid of 9 per cent with no lactic acid present.

PRELIMINARY OBSERVATIONS

The patient remained in the hospital fifteen days. During this time her diet was the same as the one she had followed recently at home with fair results. It excluded all foods which the mother thought made the patient worse. The fluid intake (including the water in the food) averaged about 3000 grams per day. The patient remained in bed and on the fifth day of her hospital stay she was found to be almost free of asthmatic breathing. She complained of no distress as far as the asthma was concerned, and so on the eighth day she was given with the noon meal 20 grams of codfish. This was prepared by soaking for one hour in water, pouring away the water, and then cooking for twenty to thirty minutes in fresh water. Later whenever codfish was given to the patient, it was always prepared in the same way.

After the administration of the codfish, there was an asthmatic attack in one hour. It continued for two hours, becoming increasingly worse until 15 minims of adrenalin were given. Following this the patient felt better, but the next day there was a delayed reaction. The patient started to have rather marked asthmatic breathing shortly after the middle of the day. Later, in the afternoon, 15 minims of adrenalin were again required.

On the twelfth hospital day the patient was again feeling fine, and this time at the noon meal 15 grams of codfish prepared as stated above, were given. In about one hour, an asthmatic attack began, and the next day there was again a latent reaction. The response of the patient to the second administration of the codfish was almost identical to that of the first instance.

FURTHER OBSERVATIONS AND RESULTS

Ten days later, after spending the Christmas holidays at home, the patient was readmitted to the hospital for further study. Chart 1 illustrates how the first twenty-six hospital days were divided into five periods, the diet and fluid intake being varied from period to period. The patient was kept in bed and carefully watched.

During the first period the diet consisted of 214 grams of carbohydrate, 132 grams of fat, and 81 grams of protein. The total fluid intake, which includes the drinking water and the preformed water of the food, varied from 2200 grams to 3500 grams. The patient had a slight attack of rhinitis, and there was a moderate amount of asthma present. This is shown on the first day of Period I of Chart 1.

The amount or degree of asthma was roughly estimated, and in Charts 1, 2, and 3 it will be seen that it was recorded in each instance in degrees. The patient was considered to have about one degree asthma when on auscultation asthmatic wheezing respiratory sounds could be

heard easily throughout most of the chest. With two degrees of asthma the patient had enough asthma to feel somewhat distressed, while with three degrees it could easily be seen that the patient was having a rather marked asthmatic attack, there being great distress with visible difficulty in breathing and with the noisy respiration audible a short distance from the patient.

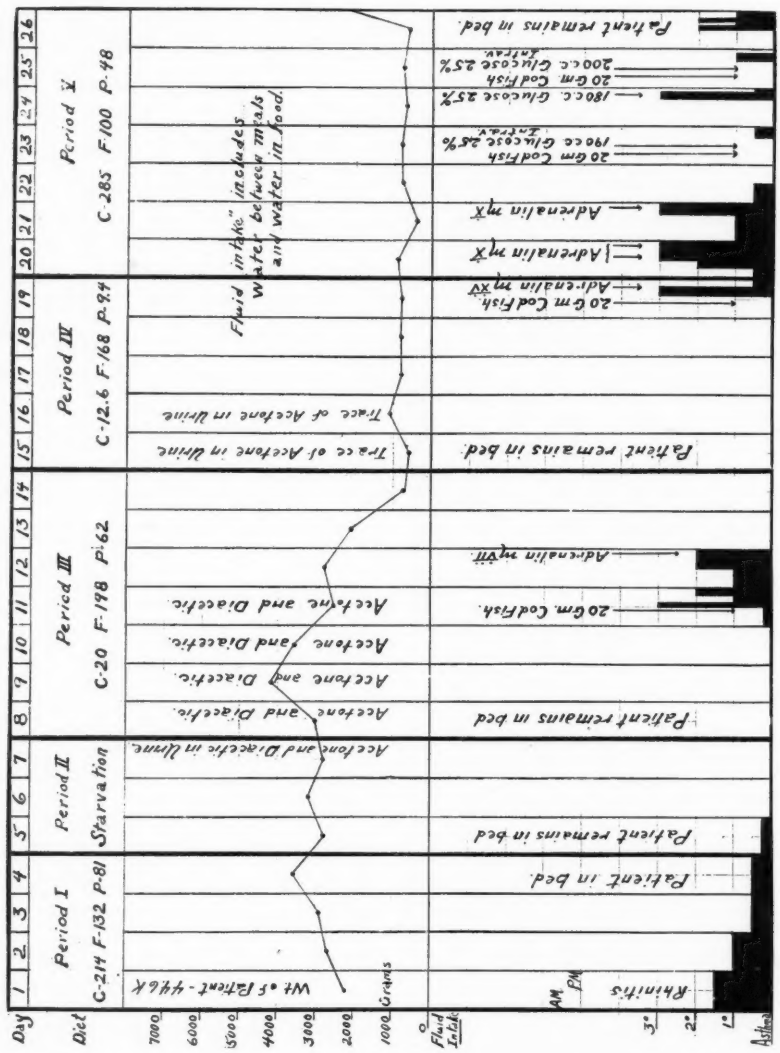

Chart 1.—Graphic representation of the asthmatic reactions when ketogenic and high carbohydrate diets were used with a low fluid intake. (Note the days on which codfish was given and also when treatment was carried out with glucose.)

During the second period, the patient became free of asthma, and she received no food, but was permitted to take about 3000 grams of water per day. This was a starvation period of three days' duration instituted to prepare for the next period, during which the patient was on a ketogenic diet—low in carbohydrate and high in fat. The fluid intake remained unchanged. Acetone and diacetic acid appeared in the urine.

On the fourth day of the third period (see Chart 1) the patient received at noon 20 grams of codfish. There was a marked reaction in about one hour which was quite severe for a little more than one hour. The next day the patient had another attack of asthma requiring 7 minims of adrenalin. The ketogenic diet with the production of acetone

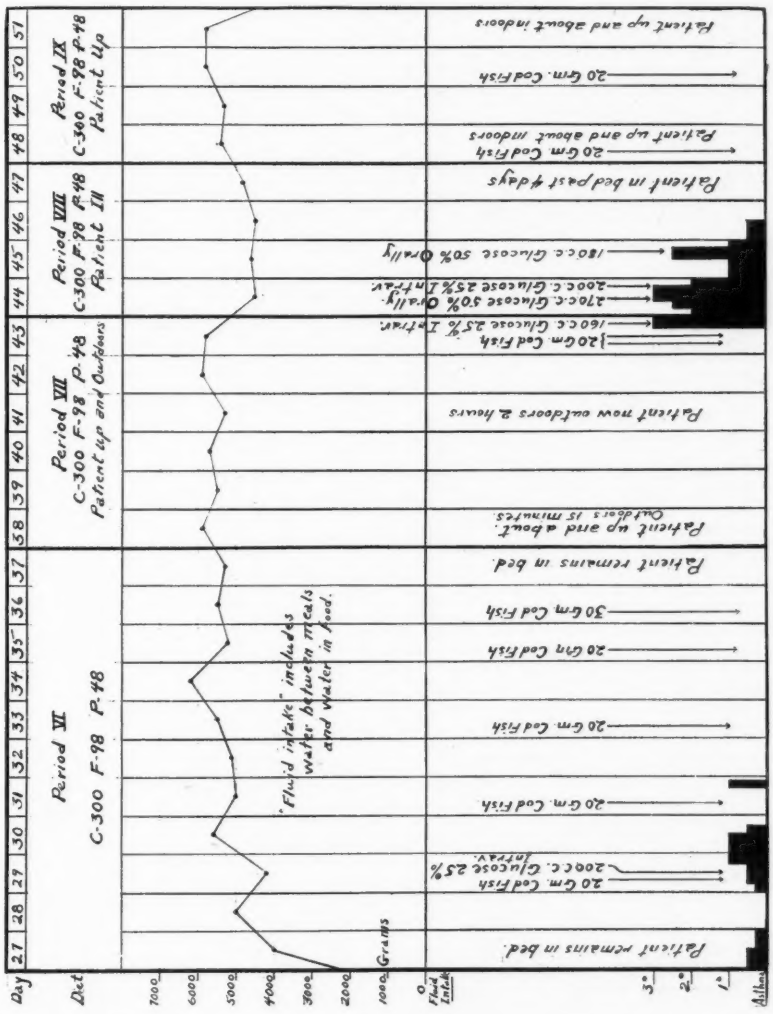

Chart 2.—Graphic representation of the asthmatic reactions when the high carbohydrate diet was used with a high fluid intake. (Note the number of times that codfish was given.)

and diacetic acid in the urine had not protected the patient against a reaction from the codfish.

During the fourth period, the diet was made still more ketogenic and the fluid intake was reduced to less than 1000 grams per day. On the fifth day of this period the administration of 20 grams of codfish was followed by a reaction which continued for three days. Adrenalin was necessary four times.

The ketogenic diet was discontinued and a diet high in carbohydrate was substituted. This marks the fifth period, and on the fourth day of this period codfish was again given. It was followed within one hour by the administration of 190 c.c. of a 25 per cent solution of glucose intravenously. The glucose was permitted to flow slowly into the vein over a period of thirty minutes. The result was interesting. Only a slight reaction occurred late in the afternoon of that day, but the next afternoon there was again the latent reaction. It was controlled, however, by giving intravenously 180 c.c. of a 25 per cent solution of glucose.

On the sixth day of the fifth period, the codfish was again given, and this was followed by a 25 per cent solution of glucose intravenously. The response was the same as on the fourth day of this period. The following day (seventh day of Period V) there was as usual a latent reaction, but the patient did not feel sick enough to require adrenalin or glucose.

Following the fifth period, the high carbohydrate diet was continued, but the fluid intake was increased so that between 5000 to 6000 grams were taken per day. This increase in fluid constitutes the sixth period which is illustrated in Chart 2.

On the third day of the sixth period, codfish was administered and followed within one hour by 200 c.c. of a 25 per cent solution of glucose intravenously. There was a slight reaction continuing into the next day. No more glucose or adrenalin was required.

Codfish was also given two days later during this period with no glucose. There was only a slight reaction. Three more times codfish was given and now there was absolutely no reaction. The high carbohydrate diet and high fluid intake were continued, but the patient was permitted to be up and about, and also to be outdoors for a short time.

During the seventh period, the time outdoors was increased from fifteen minutes to two hours, and then on the sixth day of this period codfish was given twice. The outdoor activity plus the double dose of codfish was too much for the patient, for two hours after the second administration of codfish, a severe asthmatic attack began. No adrenalin was used but 160 c.c. of a 25 per cent solution of glucose were injected intravenously with some relief. The next day 270 c.c. of a 50 per cent solution of glucose were given by mouth and later 200 c.c. of a 25 per cent solution intravenously. This was followed by a moderate amount of relief until the next day when the asthmatic symptoms became more severe, and glucose was again given orally.

Following the last day of the seventh period when the two doses of codfish were given, there were four days as is seen in Chart 2 during which the patient was ill. She had a great deal of asthma during this period (Period VIII) and she remained in bed.

On the first day of the ninth period, the patient was up and about indoors, and the codfish was tried with no reaction. Two days later,

it was repeated and there was no response. The high carbohydrate diet with the high fluid intake was able to prevent the reactions to codfish. It appears, however, that too much codfish or too much activity especially outdoors in the cold air, or both, tends to overcome this protection. This was illustrated on the last day of the seventh period (see Chart 2).

Three more periods during which the patient continued to be up and about complete this study with codfish. These periods are shown in Chart 3. During the tenth period, the fluid intake again was dropped,

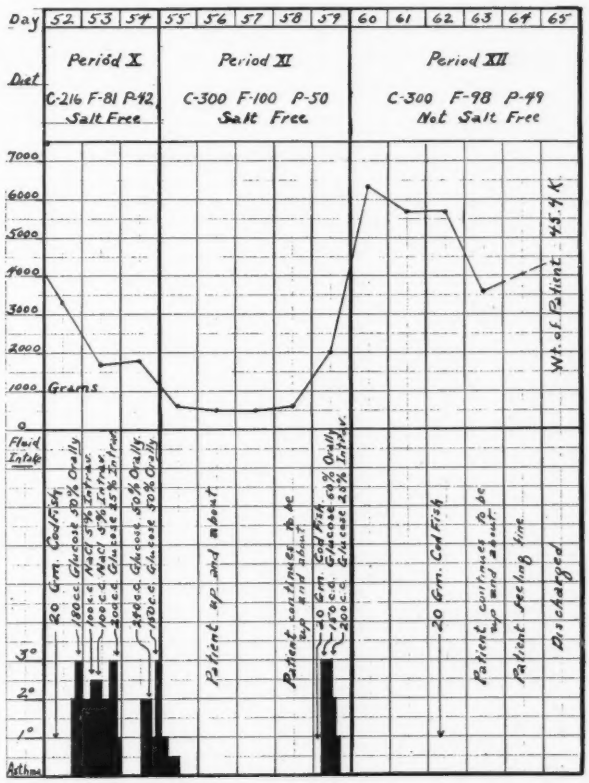

Chart 3.—Graphic representation of the asthmatic reactions when the high carbohydrate diet was used with salt restriction. (Note the effect of low and high fluid intake on the asthmatic reactions.)

and the diet was changed to one lower in carbohydrate, fat, and protein with no sodium chloride. In other words the diet was made salt free and codfish was given on the first day of the tenth period. A reaction occurred which was controlled to a certain extent by the oral administration of 180 c.c. of a 50 per cent solution of glucose.

The following day the asthma continued, and now 100 c.c. of a 5 per cent sodium chloride were given intravenously on two occasions but there was no relief. Later on the same day, the asthma became worse and 200 c.c. of a 25 per cent solution of glucose were given intra-

venously. The relief was definite. The patient slept through the night with no discomfort, and not until the middle of the next day was there another attack of asthma.

This time 240 c.c. of a 50 per cent solution of glucose were given by mouth with some relief, and later in the day 150 c.c. were again given orally. This was followed at first by a rapid decrease in the severity of the asthma, and then by a gradual decrease until it had entirely disappeared.

During the eleventh period, the carbohydrate, fat and protein were increased, but the fluid intake was decreased below 1000 grams. The diet remained salt free. Codfish was given on the last day of this period, and there was an asthmatic attack of short duration. It was controlled by the oral and intravenous administration of glucose. There was no reaction the next day, the fluid intake having been increased to 6000 grams, and the salt was not eliminated any more from the diet. This marks the twelfth and last period of observation.

During the final period, the fluid intake continued to be high; and when codfish was given on the third day of this period, there was no response. With the patient, up and about, feeling fine, it was thought best to discharge her on the diet of this period. Her weight upon discharge was 45.4 kilo.

DISCUSSION

It is evident from the foregoing results that the diet was not so important as the total fluid intake in influencing the response to codfish. The ketogenic or low carbohydrate high fat diet gave no protection. In fact with a low water intake the asthmatic attack in response to the codfish ingestion was most marked when the patient was on a ketogenic diet. The high carbohydrate diet with a moderate amount of fat offered very little protection as long as the total fluid intake was kept low but did give favorable results when the water intake was increased. The patient was quite happy on the high carbohydrate diet when she was permitted to take plenty of water, and she did not fear to take the codfish.

It will be noted that in the eighth period the patient was ill. Following all the outdoor activity of period seven she developed a definite upper respiratory infection. Other children on the Pediatric Service of the hospital were also ill with the same type of infection at that time. The high carbohydrate diet with plenty of water did not prove to be very satisfactory in controlling the asthma during the end of the seventh period and the early part of the eighth period. The infection which was present at that time probably prevented a favorable response.

It was suggested that the carbohydrate diet be made salt free, and then the water intake be reduced. This did not give any protection against the asthmatic reactions which follow the ingestion of codfish.

During this period when the patient was on a salt free diet, a 5 per cent solution of sodium chloride was given intravenously on two occasions with no relief. A 25 per cent solution of glucose was given intravenously with definite relief.

The response to glucose solution intravenously and even to the oral administration of the glucose solution is most interesting. The 25 per cent solution when given intravenously shortly after the ingestion of the codfish prevented a reaction. If a delayed reaction occurred, then another injection of the glucose solution put a rather quick stop to it. The 50 per cent glucose solution was given by mouth, and it was only effective in hastening the disappearance of an asthmatic attack. Early in any asthmatic reaction to the codfish, the glucose preparation given orally was of little value, but later after the patient had suffered for some time, the glucose solution administered by mouth shortened the attack. Severe attacks of asthma always required intravenous glucose solution, while some of the mild attacks were controlled by the oral administration of the glucose solution.

The patient always felt that the effect of the intravenous glucose was equal to that of fairly large doses of adrenalin. Although the adrenalin could be given in a few minutes, while the intravenous glucose required about thirty minutes, the patient did not ask for adrenalin because she frequently developed a severe headache after it was used. The only unfavorable response to the glucose was the development of nausea in some instances, and on two occasions vomiting occurred. The glucose given orally was as effective as small doses of adrenalin.

It is interesting to recall at this point the effect of adrenalin on the carbohydrate metabolism. The administration of adrenalin causes a rapid rise of the blood sugar which may even result in glycosuria. According to Peters and Van Slyke[3] the rise must be due to an accelerated glycogenolysis, as muscle glycogen cannot be mobilized into the blood as glucose. The question arises as to whether among other things the very fact that adrenalin increases the blood sugar is the means by which it produces its effect in cases of food allergy. Just how this temporary increase in the blood sugar acts in preventing or decreasing allergic reactions is not known. Very little allergic disease is associated with diabetes.[4] Is this because there is a tendency to a higher blood sugar? I do not wish to draw conclusions from this case and to answer this question at this time.

One of the numerous properties that ephedrine has in common with adrenalin or epinephrin is the power to produce hyperglycemia. The blood sugar reaction is somewhat slighter and slower than that which follows the use of epinephrin. This is exactly the usual response of an allergic reaction to ephedrine, that is, it is slighter and slower than that of epinephrin.

SUMMARY

An allergic individual responding to the ingestion of codfish with an asthmatic reaction was kept under close observation for a short time and the following was revealed:

1. When the patient was on a ketogenic diet with a fair amount of fluid intake, no protection against the asthmatic attacks was obtained. A high carbohydrate diet gave very little protection.

2. When the water intake was low in connection with the ketogenic diet, the reaction was worse and the same is true in case of the high carbohydrate diet.

3. When the patient was on a high fluid intake in connection with the relatively high carbohydrate diet, full protection was obtained while the patient was up and about indoors, but this failed when the patient became quite active outdoors, and later developed an upper respiratory infection.

The administration of a solution of glucose was just as effective in controlling the allergic reactions in this case as adrenalin. Severe asthmatic attacks required intravenous glucose, while the mild attacks could be taken care of with glucose which was given orally. The effect of glucose is most interesting in that adrenalin which has long been used to control allergic reactions also raises the blood sugar.

No definite conclusions can be drawn from the observations in this one case, but the results are significant enough to warrant further study in a more extensive way with other cases of food allergy. Further work will soon be in progress.

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THE ALLERGICALLY ACTIVE SUBSTANCE IN POLLEN. A CHEMICAL AND BIOLOGIC STUDY OF *Phleum pratense* (TIMOTHY) POLLEN*

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INTRODUCTION

IN OUR previous papers[1, 2] it was shown that the ragweed pollen allergen in clinical cases of ragweed hay fever was of protein nature, and it was stated that preliminary work indicated that the allergen of timothy pollen was of the same chemical nature. This paper deals with the chemical separation and identification of this substance and the biologic proof that it is the only active substance in timothy pollen.

HISTORICAL

Very little chemical work has been done on the pollens of the family *Gramineae*. Kammann[3] from a study of rye pollen concluded that a substance of the nature of a toxalbumin was the agent producing hay fever. It was not completely inactivated by heat and resisted proteolytic enzymes, although long contact with trypsin decreased its activity. A globulin fraction was found inactive. Caulfield[4] reported that a fraction of timothy pollen designated as albumin proteose was active. Bernton, Jones, and Csonka,[5] in a preliminary study determined the nitrogen distribution in extracts of timothy and orchard grass pollen and prepared fractions designated as proteose, albumin, and globulin, and reported varying activity. Moore and Moore[6] made a study of the nitrogen and solid material extracted by ether, water, salt solution, alcohol, and alkali from timothy and orchard grass pollen, and Moore, Moore, and Cromwell[7] in a study of proteose, albumin proteose, and globulin fractions of timothy pollen, concluded that there were at least three distinct antigens active in timothy hay fever. Moore and Moore[8] found that active charcoal adsorbed selectively nitrogenous material as well as the activity from water extracts of ragweed and timothy pollen and concluded that the active material of the two pollens was similar in nature. Moore and Moore[9] identified a glucoside, Dactylin, from water extracts of orchard grass and timothy pollen. Loeb[10] in a study of foxtail and orchard grass pollen concluded from proteolytic digestion of alcohol and ammonium sulphate precipitates that the active substance was either protein or only active in combination with protein. Adelsberger[11] produced anaphylaxis in guinea pigs with extracts of timothy pollen. Bouillenne and Bouillenne[12] inactivated pollen (ragweed) extracts by

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digestion with pangestine for fifty days and concluded the active material was not carbohydrate in nature.

EXPERIMENTAL

The pollen of timothy grass (*Phleum pratense*) has been used in this work. Dry ethyl ether or petroleum ether (Soxhlet extraction) removed from the whole pollen 1.7 per cent of a solid fatty material. This did not give the typical immediate urticarial skin reaction in timothy sensitive cases, but in certain individuals not necessarily subject to timothy hay fever a dermatitis was produced by patch test similar to that produced by others[13] with the fat soluble material from ragweed pollen. This fatty material was removed from the pollen to facilitate aqueous extraction, and in all the following work the petroleum ether defatted pollen was used.

I. Chemical

A. Analysis of the Defatted Timothy Pollen

The pollen was dried in a vacuum desiccator over calcium chloride.

Total volatile matter (102°)	3.4 per cent
Nitrogen (average)	3.3 per cent
Ash* (on ignition)	3.3 per cent

Qualitative tests for organic sulphur were negative.

B. Aqueous Extraction of Timothy Pollen

Preliminary extraction experiments showed that a distilled water extract of timothy pollen using 3 gm. per 100 c.c. removed practically all the active substance and only slightly less nitrogen than a sodium bicarbonate solution extract. The active material was easily water soluble, since a three hour extraction at 7° removed as much nitrogenous material and active substance as a twenty-four hour period. The P_H of water extracts of timothy pollen varied from 5.0 to 6.2, depending on the age of the pollen (see Table I). Bicarbonate extracting fluid[14] extracts of pollen had a P_H of 7.6. The faint alkalinity prevented precipitation of protein material which slowly resulted in the water extracts. Water extracts of timothy pollen gave a nonprotein crystalline precipitate after standing at 7°. This substance melted at 185-188° (corr.). It has been named Dactylin and identified as a glucoside by Moore and Moore.[9] Sodium bicarbonate extracts of timothy pollen on long standing gave a fine needle-like precipitate with a sweetish odor and giving a yellow color with sodium carbonate, and a deeper yellow color with lead acetate. It gave a green color with ferric chloride turning red on the addition of sodium carbonate, and the acetyl derivative melted at 114-116°. It was similar to the hydrolysis product of the glucoside reported by Moore and Moore.[9] These substances had no allergic activity in cases of timothy hay fever.

*The ash contained Ca and PO_4.

C. Water Extracts of Timothy Pollen of Different Seasons and From Different Localities. A Comparison With Cat-tail Pollen

All the samples had been dried over calcium chloride and kept free from moisture. The extracts were made from the petroleum ether defatted pollen, using 3 gm. of pollen per 100 c.c. of distilled water for eighteen hours at 7°. The extracts were filtered through heavy paper by suction, and the filtered volume was adjusted to 100 c.c. by adding the necessary amount of water through the filter. Total nitrogen was determined by the Kjeldahl method. Nonprotein nitrogen was similarly determined in the filtrate after precipitation of all protein with phosphotungstic acid in hydrochloric acid solution. The difference was considered the protein nitrogen. Free reducing substances were determined by the method of Allihn as described in the former paper[1] and the P_H was determined colorimetrically. Total reducing substances were similarly determined after hydrolyzing the solution with 2 per cent sulphuric acid for two hours at 100°. The use of stronger acid for hydrolysis resulted in destruction of the free reducing substance, but using 2 per cent acid, the reducing substances were slightly greater after hydrolysis, indicating some glucosidic type of material. Reducing substances are reported as per cent glucose.

The results in Table I show that the oldest pollen, 1921, contained less total nitrogen than pollen of more recent date. This may have been due to seasonal variation or auto-oxidation with a darkening in color, noticeable in old pollens and extracts. The 1931 pollens collected from different localities gave similar extracts. The reducing substances, extracted nitrogen, and material extracted were less in extracts of older pollens, while the acidity increased with the age of the pollen. An analysis of 1931 (Virginia) pollen extracted immediately after collection and again after the pollen had aged for three weeks showed that slight alteration had already taken place. A probable explanation was the oxidation of carbohydrate material, increasing the acidity and lowering the protein solubility. The extracts of older pollen contained less protein nitrogen. The activity of the extracts in direct skin tests, when diluted on a total nitrogen basis, was similar, except the 1921 pollen extract which was less active and contained less protein in proportion to its total nitrogen content.

Since extensive clinical tests by one of the authors (Cooke) had failed to show sensitivity to the windborne cat-tail pollen (*Typha angustifolia*), a comparison of cat-tail pollen and timothy pollen extract was of interest. A 200 c.c. water extract of 15 gm. of cat-tail pollen on saturation with ammonium sulphate gave no precipitate. Saturation of water extracts of such active pollens as ragweed (*Ambrosia trifida*), timothy, orchard grass (*Dactylis glomerata*), and rye (*Secale cereale*) gave a typical albuminous precipitate of the active material. A subsequent bicarbonate extract of the above cat-tail pollen at half saturation with ammonium sulphate gave a small amount of precipitate, probably globulin. Sim-

ilar distilled water insoluble material was precipitated at half saturation with ammonium sulphate from timothy, orchard grass, and rye pollen, and was inactive by skin test. This confirmed the work of Kammann[3] that the globulin of rye pollen was inactive. Water extracts of timothy and cat-tail pollen (see Table I) contained large amounts of reducing substances, but differed in that cat-tail pollen extracts contained only negligible traces of protein nitrogen, probably globulin. This confirmed the previous observation[1] that the addition of alcohol to 50 per cent concentration gave protein precipitates from water extracts of ragweed and timothy pollen, but gave no precipitate with similar cat-tail pollen extract. The inactivity of cat-tail pollen is probably due to the absence of appreciable amounts of water soluble protein which is the active material producing hay fever in all pollens so far investigated by us.

TABLE I

TIMOTHY POLLEN AND CAT-TAIL POLLEN

POLLEN	TIMOTHY	TIMOTHY VIRGINIA	TIMOTHY N. JERSEY	TIMOTHY VIRGINIA	TIMOTHY VIRGINIA	TIMOTHY N. JERSEY	CAT-TAIL N. JERSEY
SEASON	1921	1928	1930	1931	1931	1931	1930
N in defatted pollen per cent	2.94	3.25	3.41	3.51			
WATER EXTRACTS MADE FROM 3 GM. POLLEN PER 100 C.C.							
Date of extraction	June, 1931	June, 1931	June, 1931	July 10 1931	July 26 1931	July 26 1931	December 1931
Material extracted per cent	34.6	43.0	45.6	51.2	49.6	48.2	
Mg. N per c.c.	0.21	0.15	0.23	0.45	0.37	0.36	0.25
Nonprotein N mg. per c.c.	0.16	0.08			0.17		0.22
Protein N mg. per c.c.	0.05	0.07			0.20		0.03
P_H	5.0	4.8	5.5	6.3	6.2	6.0	6.2
Reducing substances as glucose per cent	13.1	18.5	22.4	23.3		24.4	21.2
Reducing substances after hydrolysis as glucose per cent	14.1	19.4	21.2	25.3		25.3	21.7
Color of extract	clear brown	clear brown	clear brownish yellow	turbid yellow	clear pale yellow	clear pale yellow	clear colorless
Activity dilution on N basis in direct skin test	++	++++	++++	++++	++++	++++	-

D. Precipitation of Active Material From Water Extracts With Alcohol

The addition of alcohol to 90 per cent concentration to water extracts of timothy pollen gave an active precipitate amounting to 4.2 per cent of the pollen. The alcoholic filtrate contained very slight activity.

Analysis of Precipitate

Nitrogen	6.1 per cent
Nitrogen (ash free basis)	7.4 per cent
Ash	17.7 per cent

Reducing substances after hydrolysis as glucose 25.0 per cent

This precipitate was active on scratch test, but relatively inactive as compared with pollen extracts or solutions of the purified material to be described. Its solubility in water was also markedly reduced. This lessening of activity and solubility together with the high nitrogen content of the precipitate indicated the protein nature of this material.

E. Successive Alcoholic Extractions of Timothy Pollen

Three gm. of 1928 (Virginia) pollen were extracted successively with 100 c.c. absolute alcohol, 95 per cent alcohol, 70 per cent alcohol and water. The extracts were analyzed and gave the results in Table II.

TABLE II

SUCCESSIVE EXTRACTION OF 3 GM. 1928 TIMOTHY POLLEN

	MATERIAL EXTRACTED PER CENT	NITROGEN MG. PER C.C.	NITROGEN* REMOVED PER CENT	FREE REDUCING SUBSTANCES AS GLUCOSE PER CENT	P_H	ACTIVITY
Absolute alcohol	22.9	0.06	0.20	10.5	4.2	–
95 per cent alcohol	9.7	0.03	0.10	7.1	4.2	–
70 per cent alcohol	13.3	0.04	0.13	4.5	4.8	+–
Water	3.8	0.02	0.06	trace	6.4	++

*Defatted timothy pollen contained 3.3 per cent nitrogen.

Timothy pollen rapidly washed with 85 per cent alcohol and dried with ethyl ether gave active water extracts containing about one-third the nitrogen of extracts of untreated pollen and when diluted on a weight basis were not so active as water extracts of pollen not washed with alcohol.

Alcohol of different concentrations removed the free reducing substances and traces of nitrogenous material and did not contain active substance. Water extracts following alcoholic treatment were very low in nitrogen and activity in comparison with routine extracts when diluted on a weight basis. A pollen residue following a water extraction contained 4.5 per cent nitrogen, while a pollen residue after alcoholic and water extraction contained 5.2 per cent nitrogen showing that alcohol had rendered nitrogenous material insoluble in subsequent aqueous extraction.

F. Separation and Purification of the Active Material

Preliminary experiments showed that saturation of water extracts of timothy pollen with ammonium sulphate gave precipitates containing all the active substance. On dialysis, using a hardened collodion membrane, the active substance remained inside the membrane, reducing substances and nitrogenous material passed through. After dialysis with an ordinary collodion membrane, some activity was present in the dialysate, but such dialysate gave a test for protein with phosphotungstic acid.

a. Purified Protein 209A

One hundred grams of the 1928 (Virginia) pollen were extracted with 600 c.c. of distilled water for six hours at 7° with frequent shaking. The pollen was filtered off and by repeated precipitation by saturation with ammonium sulphate and adjusting the P_H to 4.6 with 0.2n sulphuric acid as described in the purification of the active protein material from the ragweed pollen;[1] a final light yellow precipitate resulted. Its solution was dialyzed against distilled water until free from sulphate when a small amount of a yellow flocculent Protein Material 209G separated, and was filtered off. The clear water soluble Protein Solution, 209A, was divided and salt added to one portion to 0.85 per cent concentration when it was Seitz filtered for tests and for desensitizations. (Tables III and IV.) It contained 0.1 mg. nitrogen per c.c. The remainder of the Protein Solution 209A was evaporated in a vacuum to half volume and precipitated by adding alcohol to 90 per cent concentration. A flocculent Protein Precipitate 209A resulted which was washed with alcohol and ether and dried at 105° for analysis. Evaporation of the alcohol showed practically complete precipitation.

b. Purified Protein 222A

One hundred grams of 1931 (Virginia) timothy pollen were similarly extracted with water. After filtering, the extract was dialyzed against distilled water for twenty-four hours at 7° to remove inactive sugars, nitrogenous material, and coloring matter. The active material was precipitated from solution twelve times by saturation with ammonium sulphate, precipitation resulting from 50 to 100 per cent saturation. Each time the precipitate was dissolved in water and filtered through heavy paper to remove insoluble, slimy material before reprecipitation. In this case no acid was used to adjust the P_H, precipitation taking place from P_H 6 to P_H 7. The final solution was dialyzed free from sulphate when a small amount of a flocculent Protein Material 222G separated and was removed by filtration. The clear, colorless Protein Solution 222A was divided and salt added to 100 c.c. to 0.85 per cent concentration, when it was Seitz filtered and used for tests and for desensitizations (Tables III and IV). It contained 0.3 mg. nitrogen per c.c. Alcohol was added to the remaining 70 c.c. to 80 per cent concentration and a

white flocculent Protein Precipitate 222A separated. It was removed, washed with alcohol and ether and dried at 105°. The alcoholic supernatant was evaporated to 10 c.c. when a small amount of a similar precipitate separated which was similarly treated and added to the above sample.

c. The Proteins 209G and 222G

The Protein Material 209G which precipitated on removal of all salt by dialysis, was dissolved in salt solution and again precipitated by dialysis. The material was filtered off, washed with water and dissolved in salt solution. It contained 0.05 mg. nitrogen per c.c. and gave negative skin reactions in a series of timothy sensitive cases, except in a few very sensitive cases in which it gave slight reactions, undoubtedly due to traces of Protein 209A as shown by desensitization tests. The similar Protein Material 222G reserved for analysis contained 11.5 per cent nitrogen and was probably protein of globulin nature. A 10 per cent salt solution extract of timothy pollen following two successive water extractions, after dialysis free from salt, gave a similar precipitate of no importance in relation to activity, since a single water extraction had removed practically all active material.

G. Chemical Tests and Analyses

The Protein Solutions 209A and 222A gave the following reactions: The biuret, Millon and Molisch tests were positive. The p-dimethylamino benzaldehyde and xanthoproteic reactions were negative. A precipitate resulted with phosphotungstic acid, picric acid, trichloracetic acid and sulphosalicylic acid. They were levorotatory. Only traces of reducing substances were present before hydrolysis in Protein Solutions 209A and 222A, and the amounts after hydrolysis were increased but were still so small that such reducing substances might easily have been removed by adsorption to the protein when the solutions were cleared of protein and may have been free sugars adsorbed by the protein.

The analyses of the Protein Precipitates 209A and 222A, derived by alcoholic precipitation of the respective solutions and dried at 105°, gave the following results:

Analyses of Protein Precipitate 209A and Protein Precipitate 222A Dried at 105°

Protein Precipitate 209A

	N. Per Cent	C. Per Cent	H. Per Cent	Residue Per Cent	Reducing Substance	P
	10.90	52.08	7.67	2.38	+	–
	10.75					
Corrected for residue	11.12	53.33	7.85			

Protein Precipitate 222A

	11.28	48.13	7.24	4.97	+	−
	11.09					
Corrected for residue	11.78	50.68	7.67			

The analysis is typical for protein material. The low nitrogen and the presence of reducing substances with a positive Molisch test, indicated the material might be a conjugated protein of the nature of a glucoprotein. A water extraction of the coagulated Protein Precipitates 209A and 222A removed the reducing substances leaving a residue higher in nitrogen and free from reducing substances even after acid hydrolysis. Hence it was probable that the reducing substances were present as an impurity and not chemically combined to the protein as in a glucoprotein. An extract of the pollen contained less than 4 per cent protein and from 18 to 25 per cent reducing substances, and it was likely that the method of purification would not separate the protein from the last traces of reducing substances. The solubility in distilled water with precipitation at saturation by ammonium sulphate and coagulation by alcohol indicated the protein to be albumin.

II. Biologic

The precipitin test was negative on titration of Protein Solution 222A, 0.3 mg. N per c.c. with a very active serum of a timothy sensitive case giving skin reactions to the Protein Solution 222A.

Tests for activity of water insoluble products, such as those removed by fat solvents, were made by the scratch method on timothy sensitive cases. All such substances failed to give an immediate urticarial wheal.

Water soluble material diluted on a nitrogen basis was tested by intracutaneous injection in timothy sensitive cases. The supernatant fluid, after precipitation by saturation with ammonium sulphate, when freed of salt by dialysis, was protein free and inactive by direct skin test.

Particular importance was attached to the studies of the Protein Solutions 209A and 222A. By direct test on timothy sensitive cases these gave positive results in all cases. A 0.1 mg. N per c.c. solution of Protein 222A heated for twenty minutes in the autoclave gave by direct test only faint reactions, showing that heating did not completely destroy all activity.

Ten c.c. of Protein Solution 222A gave in the sugar analysis, 0.0115 gm. Cu_2O after acid hydrolysis. Protein Precipitate 222A derived by alcoholic precipitation was extracted with water, and the extract by direct skin test gave a questionable reaction. This solution, after acid hydrolysis, was found to be identical with the Protein Solution 222A, as far as reducing substances were concerned but it contained practically no protein. Protein Solution 209A, similarly treated, gave the same re-

sults. This indicated that the reducing fraction was not responsible for activity.

The next step was to determine whether routine timothy extracts contained any allergen other than the albumin in Protein Solutions 209A and 222A. This was carried out by the desensitization of passively sensitized skin sites—the in vivo method of transfer and desensitization, as described in our previous paper.[1]

The serum of a timothy and horse sensitive case (St) was used. One-tenth c.c. of serum was injected in each of seven sites on a normal individual. Three days later 0.05 c.c. of the solution to be tested was injected in the sites. The strength of solution is given in mg. N per c.c. Results were read in fifteen minutes. The solutions tested, the strength and results are summarized in Table III.

TABLE III

THE IN VIVO CROSS-DESENSITIZATION OF SENSITIZED SITES

JAN. 5	JAN. 8		JAN. 10				JAN. 11	
SERUM SITE	SOLUTION	RESULT	SOLUTION	RESULT	SOLUTION	RESULT	SOLUTION	RESULT
Site 1	209A 0.05	++++	209G 0.05	–			Horse 0.1	++
2	209A 0.05	++++	T31* 0.05	–			Horse 0.1	++
3			209A 0.05	++++				
4	209G 0.05	++	209G 0.05	–	209A 0.05	++		
5							Horse 0.1	++++
6	T31* 0.05	++++	209A 0.05	–			Horse 0.1	++
7			T31* 0.05	++++				

*T31 = A routine extract of timothy pollen.

This is an example of many such cross-desensitization tests with four different timothy sensitive sera and using Protein Solution 222A as well as 209A. In the above experiment it is shown that with Serum St, 0.05 c.c. of Protein Solution 209A desensitized Site 2 so that subsequent injection of 0.05 c.c. T31, the routine extract of timothy pollen, was negative, whereas the site was still active to extract of horse dander. Site 6 shows the reverse.

The in vitro method of desensitization was also employed. This procedure has been shown by Walzer and Bowman[15] to be effective and specific. An example will be cited:

A timothy sensitive serum (Serum M) was combined with serum of a case sensitive to horse dander (Serum C) and to this was added in one tube the Protein Solution 222A and in another tube horse dander extract. As control, egg white was added in place of the above antigens. The mixtures were incubated overnight and skin sites made by injection of 0.1 c.c. in each site in a normal individual previously determined to be receptive to transfer but nonreactive. Tests were made three days later. The work and results are summarized in Table IV.

TABLE IV
IN VITRO DESENSITIZATION OF SENSITIVE SERUM

	JAN. 4	JAN. 7		JAN. 9	
MIXTURE	SITE	TEST SOLUTION	RESULT	TEST SOLUTION	RESULT
I	1	T31* 0.01	–	Horse 0.05	++
I	2	222A 0.01	–	Horse 0.05	++
I	3	Horse 0.05	+++		
II	1	T31* 0.001	++++	Horse 0.05	++
II	2	222A 0.001	++++		
II	3	Horse 0.05	+++		
III	1	Horse 0.1	–	T31* 0.01	++++
III	2	T31* 0.001	+++		
III	3	222A 0.001	++++		

Mixture I Serum M 0.4 c.c. + 222A 0.1, 0.1 c.c. + Serum C 0.2 c.c. + N/1 Salt 0.3 c.c.
Mixture II Serum M 0.4 c.c. + Egg Alb. 0.1, 0.1 c.c. + Serum C 0.2 c.c. + N/1 Salt 0.3 c.c.
Mixture III Serum M 0.2 c.c. + Horse 0.1, 0.2 c.c. + Serum C 0.1 c.c.

*T31 routine extract of timothy pollen.

This procedure was used with 10 different sera on 22 normal individuals using Protein Solutions 209A and 222A. Desensitization was always effected with these purified preparations against the Routine Extract T31 of whole defatted timothy pollen. In the above experiment with Mixture I desensitization was obtained by Protein Solution 222A against itself and Routine Extract T31 but not against horse dander. With Mixture III desensitization was effected by horse dander against itself but not against the timothy preparations. In Mixture II using the protein egg white for control, desensitization was not effected against the antigenic substances. This demonstrated that the albuminous protein of timothy pollen completely and specifically desensitized the timothy sensitive serum.

The question still remained regarding the activity of the Protein Solution 209G (globulin). By direct test it gave reactions only on the very sensitive group of patients. Table III gives an example of the desensitization tests that were done. Solution 209G gave a reaction in Site 4. It did not give a reaction in Site 1 on January 10 after desensitization with Solution 209A, whereas Solution 209A gave a positive reaction in Site 4 after Solution 209G was negative, but this reaction was less than that obtained in Site 3. Such results indicate that Solution 209G contained traces of Solution 209A that could not be separated by chemical precipitation, and that Solution 209G (globulin) is not a second active substance in timothy pollen.

CONCLUSION

It has been shown by the biologic tests that the ammonium sulphate precipitate contains all the active substance. Since by desensitization test the purified albumin solution has been shown to neutralize com-

pletely, specifically sensitive serum against whole pollen extract, the conclusion is justified that there is but one active substance in timothy pollen. The trace of reducing substance was undoubtedly an impurity and not responsible for the activity, since the reducing substance, after removal of protein by alcoholic coagulation, was inactive. The slight activity of the globulin fraction has been previously explained. The chemical studies have indicated that the active substance was an albumin.

The protein nitrogen content of pollen extracts can be determined by phosphotungstic acid precipitation. Since it has been shown that the active substance in ragweed, timothy, and certain grass pollen extracts is an albuminous protein and only traces of inactive protein (globulin) are present, this procedure may offer a more accurate method for standardizing extracts. Work along this line is being investigated.

SUMMARY

1. The allergically active substance of timothy pollen is an albuminous protein similar to the active material of ragweed pollen. It has been shown to be the only active substance.

2. Water extracts of ten-year-old timothy pollen were found to be low in protein, nitrogen, and activity, as compared with extracts of new pollens.

3. Alcoholic treatment of timothy pollen greatly lessened the amount of extractable nitrogen and activity. Heating lessened the activity of extract.

4. The globulin and reducing substances have no specific activity.

5. The precipitin test was negative, using the purified albumin and a specifically sensitive serum.

6. There was no albumin found in cat-tail pollen. This may explain the absence of clinical and skin reactivity to this airborne pollen.

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THE BIOLOGIC IDENTITY OF CERTAIN GRASS POLLENS CAUSING HAY FEVER*

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INTRODUCTION

RECENT studies[1, 2] on ragweed pollen have shown that the substance producing hay fever is an albuminous protein, that it is the only active substance in the pollen and that it is biologically identical in the two eastern varieties, *Ambrosia trifida* and *Ambrosia artemisiaefolia.*

Subsequent work[3] with timothy pollen (*Phleum pratense*) has shown that the hay fever producing substance is an albuminous protein and that it is the only active substance in the pollen. An active albumin has also been recovered from rye (*Secale cereale*) and orchard grass (*Dactylis glomerata*) pollen.

These findings have opened the way to a more profitable review of the question of the possible identity of the active substance in some of the more important pollens of the *Gramineae,* and this paper presents the experiments and the conclusions that may be drawn from such a study.

HISTORICAL

There is still a great diversity of opinion on the question of the allergic identity of grass pollens, and many workers adhere to the practice of using extracts of several of these pollens. Many years ago Cooke and Vander Veer tested several hundred cases of early (June and July) hay fever with extracts of pollen of timothy (*Phleum pratense*), orchard (*Dactylis glomerata*), rye (*Secale cereale*), velvet (*Holcus lanatus*), June (*Poa pratensis*), low spur (*Poa annua*) and redtop (*Agrostis palustris*), and found that a case reacting to one was positive to all these extracts. They concluded that such pollens must be allergically identical in hay fever cases, and since 1918, timothy pollen extract only has been used in the routine treatment of cases reacting to grass pollens at the New York Hospital Clinic. Scheppegrell's[4] findings confirm this opinion, for after testing 100 varieties of grass pollens he states that "all grasses had a similar hay fever reaction." Thommen[5] reports 30 patients tested with 81 species. All gave varying degrees of positive reactions. Watson and Kibler[6] do not agree, for most of their cases reacting to Bermuda grass were negative to timothy. The literature is full of references giving the impressions and guesses of many workers, but very little careful

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work has been done. Chobot[7] showed that 10 hay fever cases were equally sensitive by direct skin and eye tests to extracts of timothy and Bermuda pollen and that desensitization of passively sensitized sites was effected by either extract against the other. Piness and Miller[8] carried out a larger series of experiments. Contrary to the findings of Cooke and Vander Veer and of Scheppegrell and of Thommen, they found 109 cases out of 599 tested that reacted to one grass pollen extract and were regarded as negative to nine other grass pollen extracts. But they considered reactions as "positive only if classified as three- or four-plus." The correctness of excluding the minor reactions might well be questioned. In the series of desensitizations carried out on passively sensitized sites, these authors showed that with four of the sera desensitization could be accomplished by Bermuda pollen extract against timothy but not by timothy against Bermuda, and with three other sera it was effected by timothy extract against Bermuda but not with Bermuda against timothy. With no single serum was desensitization effected by both extracts against the other. This is contrary to the findings of Chobot and, as will be seen, to our present findings. Attention should be called to their serum B experiments, where timothy extract could desensitize against Bermuda in two recipients but could not in the other two.

EXPERIMENTAL

For this study we selected pollens of the following grasses:* Timothy (*Phleum pratense*), Bermuda (*Cynodon-Capriola dactylon*), Johnson (*Sorghum halepensis*), orchard (*Dactylis glomerata*), June (*Poa pratensis*), redtop (*Agrostis palustris*) and rye (*Secale cereale*).

The routine extracts of these seven grasses were prepared from dry-ether defatted pollen. Three grams of pollen were extracted in 100 c.c. of alkaline salt solution for eight hours, filtered through a Seitz filter and standardized on a nitrogen basis. Preparations T209 and T222 are solutions of the purified albuminous protein from different lots of timothy pollen. They were obtained by ammonium sulphate precipitations from water extracts as elsewhere described,[3] and analysis showed them to be comparatively pure. The sera used in this work were obtained from cases with clinical hay fever of the early (June and July) type. Continued testing of such patients confirmed the earlier observation of Cooke and Vander Veer that patients reacting to one grass pollen extract also react with but minor variation to the extracts of the others here studied. We could not find any such cases as the 109 reported by Piness and Miller as giving reactions to but one grass pollen.

Desensitization tests in vivo had already shown[3] that the purified Protein Solutions T209 and T222 would completely desensitize sites

*With exception of Bermuda and Johnson grass, the pollens were specially collected for this work by our botanist Mr. Hodgson in the summer of 1931. The pollens of Bermuda and Johnson grass were purchased from Greer and Co.

against routine timothy extracts in all cases tested. This was also found to be the case in the desensitization tests in vivo with the other grass pollen extracts used in this study. Details need not be given.

In 1930 Walzer and Bowman[9] reported the use of a test tube neutralization method. Our observations with this procedure bear out the claim that it is less time consuming and avoids the continued irritation of the skin by wheal formation during the process of desensitization. With some reservations as to its general applicability it is the method of choice for such a series of comparisons as is contemplated here.

The sera of 11 sensitive cases were studied in 27 experiments carried out by this method. Since results were identical for all the sera, the details of one test series only need be given. Serum M was obtained from a case of early hay fever reacting on test to all extracts employed. Serum C is reactive to horse dander and was added to control the question of site refractoriness or nonspecific inactivity.

The following mixtures of Serum M and antigen and Serum C were made, allowed to stand at icebox temperature for twelve hours and injected in amounts of 0.1 c.c. in each site in 9 previously selected nonsensitive but receptive donors.*

Mixture		
I	Serum M 0.4 c.c. + T 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
II	Serum M 0.4 c.c. + T209 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
III	Serum M 0.4 c.c. + T222 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
IV	Serum M 0.4 c.c. + Ber. 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
V	Serum M 0.4 c.c. + Johns. 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
VI	Serum M 0.4 c.c. + Orch. 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
VII	Serum M 0.4 c.c. + Poa 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
VIII	Serum M 0.4 c.c. + R. top 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
IX	Serum M 0.4 c.c. + Rye 0.1	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
X	Serum M 0.4 c.c. + Egg 1-100	0.1 c.c. + Serum C 0.2 c.c. + N/1 NaCl 0.4 c.c.
XI	Serum M 0.4 c.c. + H. Ep. 0.1	0.4 c.c. + Serum C 0.2 c.c. .....

The proportions only of Control Mixtures X and XI are given—obviously it required more of these solutions for the nine skin donors tested. Donor I: Right arm, 10 sites of 0.1 c.c. each of Mixture I; left arm, 10 sites from Mixture X as control and on the thigh 2 sites from Mixture XI of 0.1 c.c. each. At the end of three days the first series of tests was made. All tests contained 0.05 c.c. Attention is called to the fact that pollen tests on the right arm were ten times as strong as those on the left. The figures after each extract represent its strength expressed in mg. of nitrogen per c.c. The tests and results on Donor I are shown in Table I.

Donor I had received in his left arm a serum that is shown to be reactive to each of the grass pollen extracts under study, including the purified protein preparations T209 and T222. The mixture injected in the right arm had been previously treated with routine timothy extract.

*The term "donor" as used here and in the balance of this paper refers to those individuals who donated normal skin for tests. It does not refer to those individuals whose serum was taken for study.

These sites when subsequently tested failed to react to any of the grass pollen extracts but did react to horse dander. These sites when tested with horse dander two days later all reacted. Routine timothy extract had destroyed the sensitizing capacity of this serum for *all* the pollen extracts used but not for horse dander. In Mixture XI the sensitizing capacity of the serum for horse dander was specifically destroyed, since subsequent tests with timothy pollen gave positive reactions.

TABLE I

Date: Jan. 4	Jan. 7		Jan. 9	
Rt. Arm: Mixt. I	Test	Result	Test	Result
Site 1	T 0.01	Neg.	H. Ep. 0.05	+++
2	T209 0.01	Neg.	H. Ep. 0.05	+++
3	T222 0.01	Neg.	H. Ep. 0.05	+++
4	Ber. 0.01	Neg.	H. Ep. 0.05	+++
5	Johns. 0.01	Neg.	H. Ep. 0.05	+++
6	Orch. 0.01	Neg.	H. Ep. 0.05	+++
7	Poa 0.01	Neg.	H. Ep. 0.05	+++
8	R. top 0.01	Neg.	H. Ep. 0.05	+++
9	Rye 0.01	Neg.	H. Ep. 0.05	+++
10	H. Ep. 0.05	+++		
Lt. Arm: Mix. X				
Site 1	T 0.001	++++		
2	T209 0.001	+++		
3	T222 0.001	++++		
4	Ber. 0.001	++++		
5	Johns. 0.001	++++		
6	Orch. 0.001	++++		
7	Poa 0.001	+++		
8	R. top. 0.001	++++		
9	Rye 0.001	+++		
10	H. Ep. 0.05	+++		
Thigh: Mixt. XI				
Site 1	H. Ep. 0.05	Neg.	T 0.01	++++
2	H. Ep. 0.1	±	T 0.001	++

In the same way Donor II was injected with Mixture II on the right arm (10 sites of 0.1 c.c. each) and Control Mixture X on the left arm (10 sites) and Mixture XI (2 sites) on the thigh. Donor III was injected with Mixtures III, X and XI, and so on, each of the 9 donors receiving one of the Mixtures I to IX on the right arm and controls on the left arm (10 sites Mixture X) and thigh (2 sites Mixture XI), as stated.

The tests and results were uniformly identical throughout, exactly as stated for Donor I. Each of the nine pollen extracts desensitized this active Serum M against all other pollen extracts but did not neutralize the antibody of Serum C for horse dander. Horse dander desensitized against itself (Mixture XI) but not against pollen. The nonspecific egg white produced no desensitizing effect.

The desensitizations or neutralizations were specific. Since Protein Solutions T209 and T222 contain a single chemical pollen ingredient—albumin—and since these preparations were as effective in neutralizing Serum M as were the routine extracts, the conclusion is justified that the pollen extracts are identical in their neutralizing and desensitizing capacity and depend upon a single chemical constituent in the extract. The capacity of these grass pollen extracts specifically to react and desensitize and neutralize in the same way certainly indicates the biologic if not the chemical identity of the active substance in each of them.

CONCLUSION

The results of our experiments together with an extensive clinical experience of fourteen years in the treatment of grass pollen sensitive cases with timothy extract alone lead us to believe that in all respects the active substance of these grass pollens is a single substance and is common to all the extracts.

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THE RAGWEED SEASON OF 1931*

Third Annual Atmospheric Survey

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RECENT clinical literature on allergy[1, 2] continues to emphasize the importance of basic botanical information in the study of hay fever. It is now recognized that a knowledge of the local pollen content of the air is essential to pollen therapy.[3, 4, 5] In the case of ragweed and other widely distributed species, much of the value of careful individual atmospheric observations is lost unless the resulting picture can be fitted into the national panorama. Likewise, each succeeding nation-wide study increases our comprehension of the greater problem. A regional problem demands regional methods, and a perennial menace requires perennial, and ultimately, average statistics.

METHOD

In these annual studies[6, 7] of which this is the third, the oil coated slides are exposed daily during the ragweed season by observers at selected United States Weather Bureau† stations and at a few of the stations of the Canadian Meteorological Service. In counting the pollen on the exposed slide, such a unit area of slide surface is counted (1.8 sq. cm.) that the figure will represent the number of pollen granules per cubic yard of air. In all, during the three years more than 6,000 uniform slide exposures have been made in 51 cities in the United States and Canada, resulting in a total of 103 seasonal ragweed pollen records. All national comparisons and correlations in this paper are based on the data from 21 selected cities in which these studies have been carried on during all three seasons. The 1931 study includes a few new stations, but no changes have been made in methods of exposure or counting, most of the exposures having been made by the same men year after year and all counting being done by me.

QUANTITY

Measured by the total amount of pollen found on the slides, the ragweed pollen crop for 1931 was 66 per cent greater than that of the previous year and practically the same as for 1929. It is hardly likely that we shall find another growing season as generally unfavorable as the drought year of 1930, but it is altogether likely that subsequent studies will record a heavier total incidence than has been encountered

*From the Biological Laboratories of Abbott Laboratories.

†Acknowledgement is again made of the valuable cooperation of the U. S. Weather Bureau observers through the courtesy of their chief, Dr. Charles F. Marvin; also of the observers of the Canadian Meteorological Service, through their director, Dr. J. Patterson.

thus far. The tentative conclusions stated in a previous paper[8] that July rainfall is the most important single factor influencing the ragweed crop, is strengthened by the experience of the past season. Probably 75 per cent of the size of a ragweed plant at the time of pollination is attained during the month of July. The July rain index is not always dependable for local prediction, but I believe it is useful for a general estimate of the approaching season.

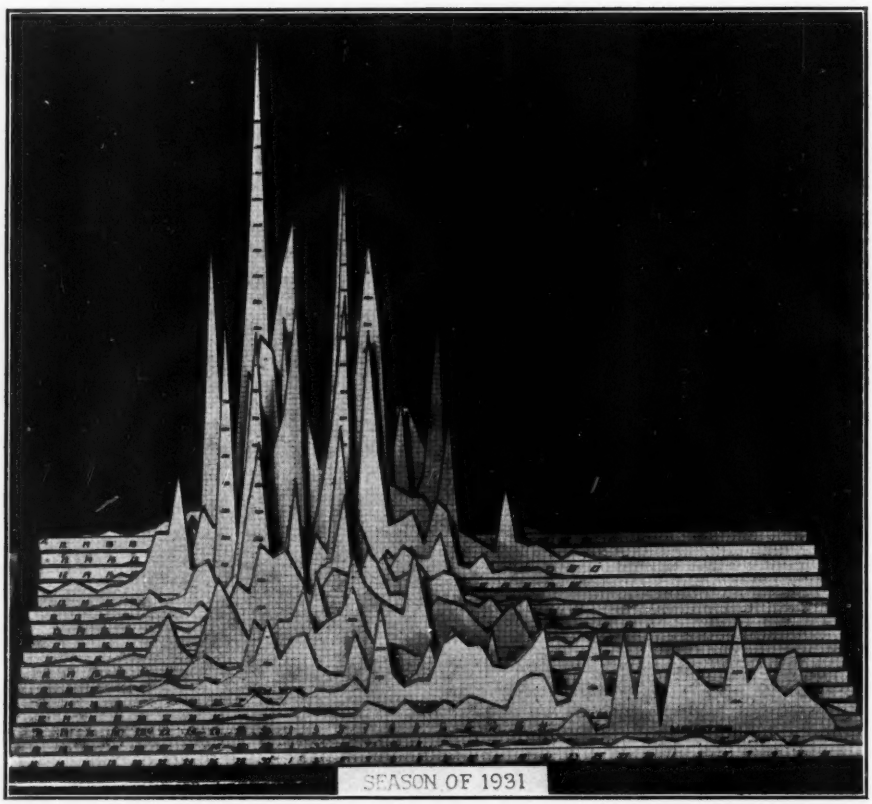

Fig. 1.—The ragweed season of 1931. Less than half of the graphs are shown. The one at the front of the group is for Tampa. The highest point (2,000 pollen granules per cubic yard of air) is for July 29, at Buffalo. Three of the next highest points are also for Buffalo, one for Milwaukee, and one for Louisville. Note the later season at Memphis and the much later one at Houston.

REGIONAL SEVERITY

As will be seen by the accompanying map (Fig. 2), the center of heaviest ragweed pollen concentration has shifted eastward during the three seasons studied. From data in hand before the beginning of this study, it seemed that Oklahoma was the center of the ragweed area. Whether or not the available figures (1926) were reliable, the carefully controlled, uniform data obtained during the last three years have shown the heaviest atmospheric pollen concentration to be successively in Missouri, Indiana, and western New York. So it is only fair

to call attention to the fact that residents of Philadelphia encountered more ragweed pollen during the past August and September than did the residents of Oklahoma City. Washington was also harder hit than Oklahoma City, and New York City almost as hard. This shift in regional severity is the outstanding feature of this third study. The condition is probably very unusual and is easily accounted for by the fact that the drought was almost as severe in Kansas, Nebraska

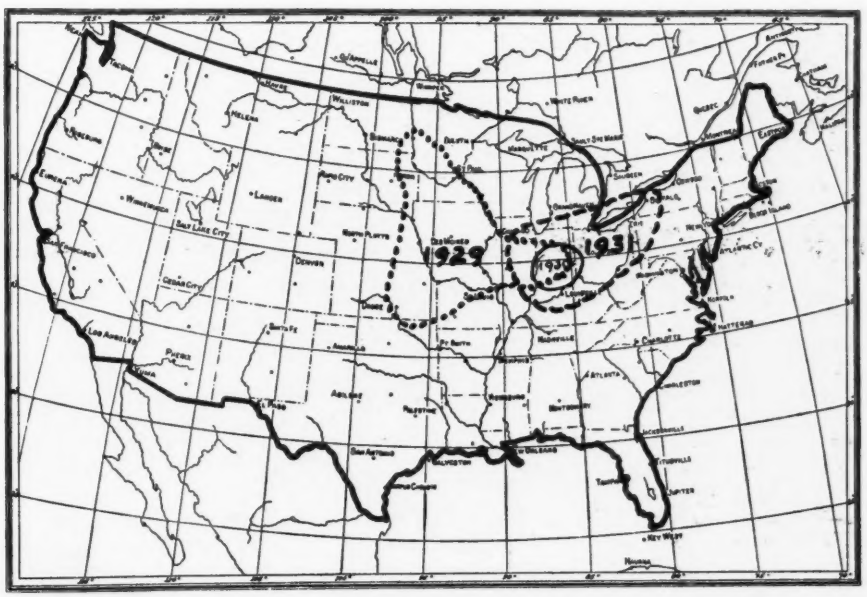

Fig. 2.—This map shows the shift of the center of the area of heaviest ragweed pollen incidence during the past three years due to two very dry summers in the midwest.

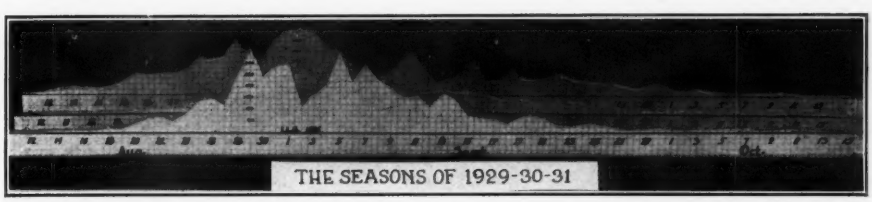

Fig. 3.—The ragweed seasons of 1929, 1930, 1931. These average graphs are on the same scale as all others shown. A midseason storm in 1931 left a gap through which may be seen the low apex of September 2, 1930, just one-half as high as August 29, 1931.

and Oklahoma as it was the previous year, while in the East, conditions during the summer were unusually favorable for ragweed growth.

BEHAVIOR OF THE SEASON

Most of the pollen found on the slides is deposited during the last week of August and the first two weeks of September (see Fig. 3). Wind and weather conditions during this time are, therefore, of the greatest importance in the distribution of whatever pollen may be at the

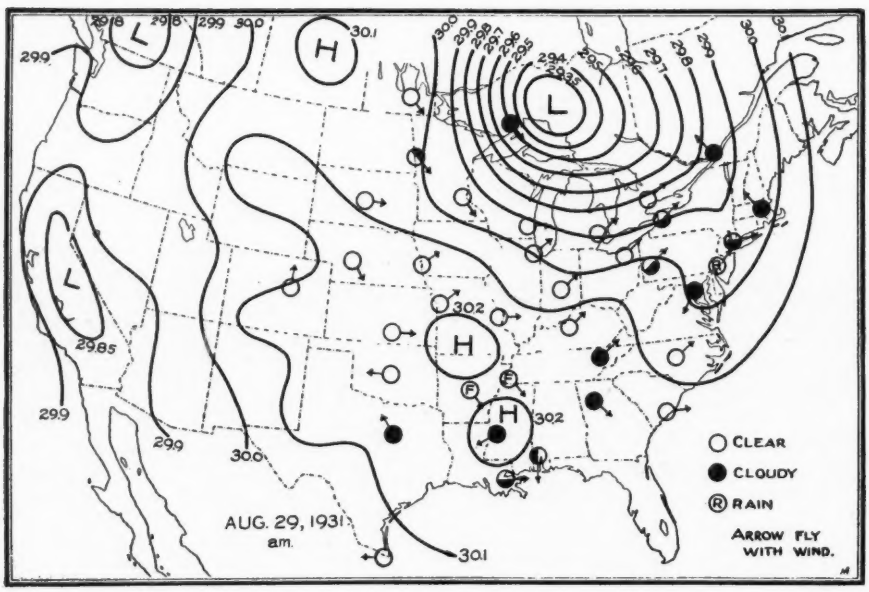

Fig. 4.—Weather conditions on the day of highest pollen concentration during the three years of the study. The isobars denote barometric pressure. The state of the sky is shown for 8 A.M. (Central Time) at each weather station used in the survey. The strong prevailing winds were from the southwest.

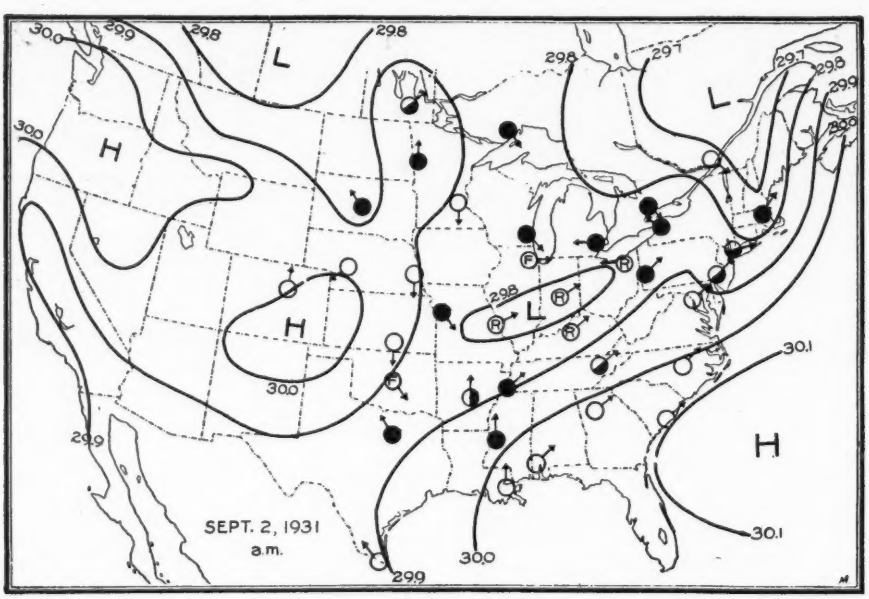

Fig. 5.—Weather conditions on a day of very low pollen concentration during the height of the pollinating season. It will be seen that the weather was adverse at most of the stations. Wind velocities were low.

point of maturity. In this past season, the last week of August was marked by unusually high winds so that even with unfavorable weather (clouds and interfering rain) maximum pollen concentrations were reached. During the next two weeks while the wind velocities were not particularly high, weather conditions were ideal for the maturing of pollen. There was continuous sunshine with almost no rain throughout the ragweed area, resulting in a series of high daily average concentrations.

Fig. 6.—The ragweed pollen seasons of 1929, 1930, 1931, at Philadelphia. Unfortunately, in keeping the seasons in order, the last season almost covers up the other two.

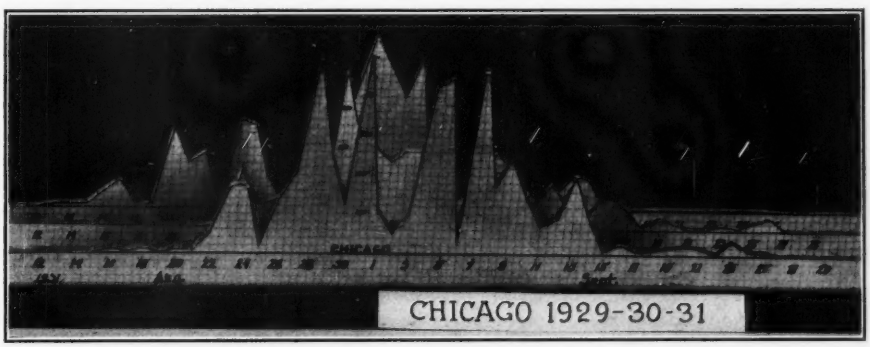

Fig. 7.—The ragweed pollen seasons of 1929, 1930, 1931, at Chicago. The 1931 record is unique in having four almost equal peaks. A combination of rain and lake breezes caused the drop of September 2, and on September 6 there was a steady northeast wind (off the lake) without rain.

The apex of August 29 was especially interesting. The extremely high pollen concentration was due to an unusual combination of favorable weather and very strong wind. On the accompanying weather map (Fig. 4), it will be seen that wind directions were almost uniformly from the southwest, clouds and rains interfering at only two stations—Boston and Philadelphia. The sudden drop in the curve on September 2 (Fig. 5) (the apex date of the two previous years) was due to the reverse conditions—a drop in wind velocity and decidedly unfavorable weather.

TYPICAL REGIONAL RECORDS

Since it is impossible in the scope of this paper to present either in graphic or tabular form, all the interesting accumulated data, only

typical records are chosen for discussion and graphic presentation. The picture of the three seasons in Philadelphia (Fig. 6) is typical of that of the other cities of the North Atlantic Seaboard. The doubling of pollen incidence in this district resulted in a very severe hay fever season, as is attested by all physicians in the eastern cities who are specializing in allergy. The result is well expressed by Dr. Clarke[9] of Philadelphia, "As for the season, it was the worst I have even seen. We had ample rain all summer, with luxuriant plants. Then we had clear dry weather through the pollinating season. The clinical course of the untreated patients amply bears this out. The treated cases, I am glad to say, did not do proportionately poorly." The 1931 increase was not so great in all of the Great Lakes and central Mississippi area as in the seaboard cities and Buffalo, but was considerable, and is very

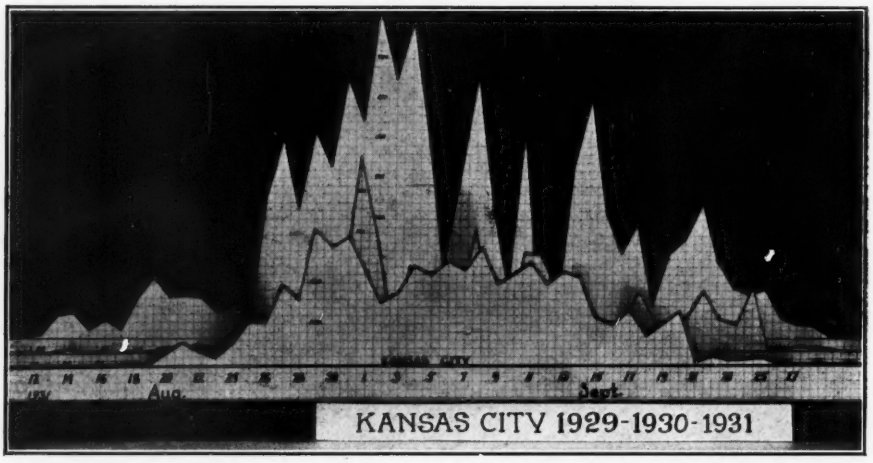

Fig. 8.—The ragweed pollen seasons of 1929, 1930, 1931 at Kansas City. The 1931 records of Kansas City lack the extreme fluctuations noted in 1929 and found in other cities such as Buffalo and Louisville during the present season.

well represented by the Chicago (Fig. 7) graph. Kansas City (Fig. 8), like most of the cities west of the ninety-fifth meridian, suffered from the drought, resulting in pollen concentrations only slightly heavier than those of the previous year.

UNUSUAL FINDINGS

One of the most interesting items in the past season's work is the extreme concentrations at Buffalo (Fig. 9) where the season was more than three times as severe as either of the two previous ones. Here a count on August 29 of 2,000 pollen granules per cubic yard of air was not only a maximum for this station but for all stations. It is interesting to note that this peak was caused by the highest wind record yet encountered. The wind blew mostly from the west, averaging 32 miles per hour for the twenty-four hours and reaching 50 miles per hour at one time. It is possible that the pollen came from Ontario.

The length of the ragweed season in Brownsville, Texas, also deserves special comment. Toxic concentrations appeared as early as mid-July and continued until late in October with a number of days of high counts

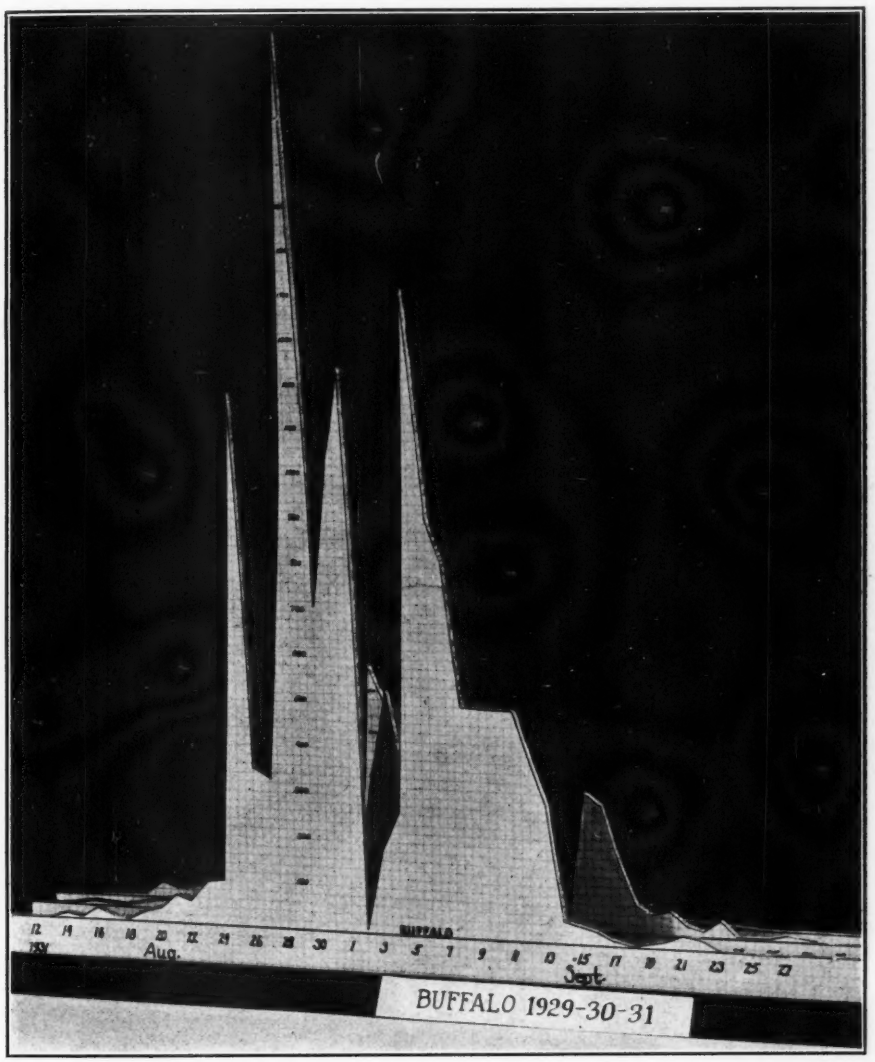

Fig. 9.—The ragweed pollen seasons of 1929, 1930, 1931, at Buffalo. Except for the extreme drop in pollen concentration on September 2, 3, and 4, 1931, it would be impossible to see the apices for the two previous years.

about the first of September. Thus the season was about three and a half months long. Nothing like it has been encountered anywhere else.

CANADA

Ottawa, Montreal, Toronto and Winnipeg experienced an average increase of 100 per cent in pollen incidence over 1930, but still this record

remained far below that of the cities of the northern states. Attention should again be called to the striking contrast between pollen concentration in Toronto and Buffalo. Though these cities are only 60 miles apart, and though their seasons are quite similar in time and date of fluctua-

TABLE I

ANNUAL RAGWEED POLLEN RECORDS

CITY	APPROXIMATE LENGTH OF SEASON IN DAYS	TOTAL POLLEN COUNT 1929	1930	1931
Amarillo	40	....	....	98
Atlanta	43	1437	1284	2408
Boise	27	332	....	....
Boston	26	582	707	1169
Brownsville	105	....	....	3159
Buffalo	35	4202	3948	14675
Charleston	45	....	....	373
Chicago	35	4132	3046	5018
Cleveland	35	3214	2646	5184
Dallas	54	4634	2569	3606
Denver	37	1767	675	965
Detroit	35	....	2193	3901
El Paso	30	110	....	....
Houston	46	.....	5278	4055
Indianapolis	40	11439	7115	9998
Jacksonville	75	....	205	....
Kansas City	50	12806	4055	5492
Knoxville	41	....	2782	3254
Little Rock	50	....	....	2024
Los Angeles	30	32	....	....
Louisville	46	....	3934	11355
Memphis	50	4580	2977	3623
Miami	0	8	....	....
Miles City	15	248	....	....
Milwaukee	35	....	....	7458
Minneapolis	45	....	2596	3674
Mobile	60	....	....	228
Montreal	28	....	439	740
Moorhead	33	6267	3501	3946
New Orleans	66	1090	1982	1350
New York	31	1196	1100	2643
North Platte	30	....	722	372
Oklahoma City	56	6309	3360	3115
Omaha	50	12085	3790	5936
Ottawa	28	....	....	459
Philadelphia	40	1799	2040	3514
Pierre	30	....	388	313
Pittsburgh	35	2499	1828	5734
Port Arthur	14	....	....	226
Prince Albert	0	....	6	....
Raleigh	35	557	929	1786
St. Louis	46	5686	3487	5573
Salt Lake City	33	....	313	....
Sault Ste. Marie	26	500	....	....
Seattle	0	0	....	....
Tampa	50	....	....	582
Toronto	35	....	581	1357
Vicksburg	50	....	....	1355
Washington	46	1956	1241	3933
Wichita	59	10123	3979	4009
Winnipeg	14	....	130	252

tion, Buffalo had eleven times as much pollen as Toronto. At Port Arthur, Ontario, slides had almost no pollen except on five days of the second week of September, while the pollen storm was raging in the United States. There is a possibility that this pollen was brought from a considerable distance southwest of Port Arthur.

THE SOUTHERN STATES

The unusual conditions of the past two seasons in the midwestern districts are fairly reflected in the adjacent areas of the south. Thus, pollen production in the southeastern part of the United States showed a considerable increase over the year before, while Texas and Oklahoma were again short. Three new gulf stations were added this season—Brownsville, Mobile and Tampa—and the latter two show very low pollen concentration. Whether or not the results from these two stations are typical, is impossible to say.

UPPER AIR INVESTIGATION

To learn something of the influence of a large body of water on the distribution of pollen, exposures were made from airplanes at North Chicago, on September 2. This investigation was made possible through the courtesy of Mr. F. C. Meier, of the United States Department of Agriculture. The wind was blowing from N.W. and N.N.W. at a surface velocity of 2 miles per hour and at 4,000 feet, 10 miles per hour. A double flight was made, one being over the land northwest of North Chicago and the other over the lake, 30 miles east of North Chicago. Exposures were made at various levels up to 4,000 feet. On this day, it was found that the bulk of the pollen over the land was below 1,500 feet, although a small amount was encountered as high as 8,000 feet. Over the lake, a heavy concentration was found at 2,000 feet and what seemed to be a separate pollen cloud at 100 to 500 feet. The totals of the two series of slides showed that midway across Lake Michigan, the air contained about 85 per cent as much pollen as existed over the land. No doubt, descending air currents drop a large amount of pollen into the lake, but it is altogether probable that a considerable amount finds its way across.

Thus each season's work fills in the gaps in the still incomplete picture of a situation whose understanding involves the comfort and usefulness of two million, otherwise healthy, persons. It is planned to continue the studies for at least two more seasons.

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A CASE OF PHYSICAL ALLERGY. A LOCALIZED AND GENERALIZED ALLERGIC TYPE OF REACTION TO COLD*

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HISTORY of Illness.—The patient is a sturdy boy, aged eight and one-half years, weighing 52 pounds, and was first seen on June 19, 1931.

He complained that within a few minutes of putting his hands in cold water they became pink and swollen and so extremely itchy that he used to cry. The consequent scratching caused large wheals to appear. Within ten minutes of immersion the hands were brawny, red and itchy, and swollen to more than twice their usual size. Consequently he was unable to flex his fingers and make a fist on account of the stiffness and pain. During the night an irritating cough or a definite cold generally ensued. These symptoms were noticed first about two years previously, and were getting progressively more severe, especially during the winter months.

As an infant he had been fed on "Ambrosia" from birth, and at two months of age was admitted to London Hospital on account of "gastric trouble." Up till the age that the present symptoms began (six and one-half years) he had suffered since birth from recurrent attacks of bronchitis, every two or three weeks, which were most pronounced during the winter months. He had contracted measles at two years and whooping cough at four years. He had always suffered from nocturnal enuresis with occasional lapses during the day, and for the previous two to three months he had complained of severe pains in the limbs which frequently made him feel very weak and faint.

Family History.—The boy is the second child of seven. The elder brother, aged ten years, suffers from asthma as well as his younger brother, aged seven. Three girls, aged six, five and four years, suffer from recurrent colds, but a definite wheeziness has never been detected. The fourth girl, aged eighteen months, suffers from severe asthma. The patient's father, his father's only sister, and his father's mother all suffer from asthma, as well as the patient's maternal grandfather.

Examination.—The patient is well nourished, roguishly intelligent and very strong. Beyond a pair of somewhat enlarged and septic tonsils there is very little abnormal to be detected in his general physical examination.

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*From The Asthma Clinic, at The Hospital for Sick Children, Great Ormond Street, London, W. C. 1.

One hand was placed in iced water at a temperature of 45° F. for four minutes, when the patient complained of a slight itchiness in the palm. There were slight swelling and redness present, and a definite raised edge at the wrist indicating the upper level of the water. The hand was taken out of the water at this time. The swelling and redness increased, and within a few minutes the hand was very hot to the touch and flexion of the fingers difficult. After a further five minutes' observation linear whealing appeared, spreading up the arm from the thickened edge toward the axilla, obviously along the lymphatics, which became red, raised, thickened cords. After eight minutes the face and ears became very red and hot, and shivering occurred. The patient complained of areas of intense irritation over his back and legs. At each of these sites an urticarial wheal appeared. His axillary temperature had dropped 1.6 degrees, his blood pressure 20 mm. of mercury, and the pulse quickened without noticeable alteration in respiratory rate. Slight headache, faintness and difficult breathing followed, and were succeeded by a steady running of the eyes and nose. Within half an hour the symptoms had subsided except for a slight cough which persisted until the next morning. Placing the same hand again in iced water two hours later was associated with a very mild recrudescence of the local symptoms.

The mucous membranes were unresponsive, for the sucking of ice did not cause swelling or irritation. The phenomenon was essentially a cutaneous one. The colder the water and the longer the period of immersion the more intense was the reaction. Similar symptoms could be produced by the subcutaneous injection of 0.2 mg. of histamine, or spraying for a minute with ethyl chloride. No urticarial effect was produced when the hand was immersed in water at 120° F. for five minutes, and immediately plunging it into ordinary tap water at 70° F. for five minutes more. The second immersion was decidedly cold compared with the first, thus excluding any psychological factor.

It was interesting to note that if the return of blood and lymph from the forearm was prevented by the application of a tourniquet, in spite of a well-marked local reaction, no general reaction ensued until the tourniquet was released. The repeated exposures to cold, while increasing the incontinence, were never associated with any hemoglobinuria.

Investigations.—The Wassermann reaction was negative. Fractional gastric analysis showed a very low delayed curve of free hydrochloric acid, which was entirely absent in all specimens obtained during the first hour and three-quarters. The adrenalin test of liver function showed a normal rise in blood sugar. The biochemical and hematologic findings before and after immersion in the water and before and after the subcutaneous injection of 1 mg. of histamine are grouped in Table I.

In Table I it will be noted that following the immersion of the hand in the iced water the few eosinophiles which were present beforehand

in the blood of the finger of the hand not immersed were not present after. The disappearance of eosinophiles from the general circulation and their concentration at the site of allergic reactions have been noted repeatedly in other conditions of allergic nature in children, so it was decided to contrast the blood counts obtained from the hand immersed and the free hand on another occasion. Four per cent of eosinophiles were found in the hand immersed and nil in the other hand, as compared with the 2 per cent which were present in each hand before the reaction. Though the numbers are small the general principle is obvious.

TABLE I.

	BEFORE IMMERSION	HALF HOUR AFTER	BEFORE HISTAMINE	25 MINUTES AFTER
Blood biochemistry				
Plasma bicarbonate	0.0276	0.0254	0.0270	0.0263
Plasma chlorides	0.600	0.574	0.590	0.572
Whole blood chlorides	0.474	0.417	0.482	0.487
Cell chlorides	0.281	Trace of hemolysis	0.267	0.305
Urine biochemistry				
Chlorides	0.980	0.705		0.860
"Proteose"	—	Trace		—
Blood examination				
R. B. C. per c.mm.	5,540,000	6,010,000	4,104,000	4,704,000
W. B. C. per c.mm.	11,500	13,900	11,600	9,350
Differential per cent				
Polymorphs	40	55	29	32
Lymphocytes	55	44	65	63
Monocytes	3	0	4	2
Eosinophiles	2	0	2	2
Basophiles	0	0	0	1
Hemoglobin	92	93	85	95

Desensitization by Histamine.—The solution used contained 1 mg. of histamine to each cubic centimeter, obtained by dissolving one tablet (0.003 gm.) of ergamine acid phosphate (Messrs. Burroughs Wellcome & Co.) in one cubic centimeter of normal saline. Subcutaneous injections were given daily, the dosage being increased from 0.1 mg. of histamine to 0.9 mg. by daily increases of 0.05 mg. The 0.9 mg. dose was repeated on four consecutive days, and the dose of 1 mg. on five successive days. The total amount of histamine given was 16.2 mg. in 25 injections over twenty-seven days.

Ample opportunity was afforded of observing the characteristic reaction of the body to histamine, especially as such large doses were used. Within two minutes of the injection the face and ears began to redden due to the dilatation and filling of the peripheral capillary bed. With the larger doses there were a decided shivering and a faintness as the brain and tissues generally suffered from oxygen lack owing to the impaired blood supply caused by the paralysis of the capillaries

and their increased permeability. In the man arteriolar dilatation also occurs. A large urticarial wheal develops at the site of the injection and the skin temperature rises while the rectal temperature falls. The blood pressure showed a marked fall of 45 mm. of Hg in the systolic and 25 mm. Hg in the diastolic pressure within eight minutes, with a return to normal in a quarter of an hour. No appreciable change was noted in the respiratory rate. The drop in blood pressure was associated with intense headache and a rise in pulse rate, and all the obvious symptoms had passed off within twenty minutes, due, in all probability, to the stimulation of the secretion of adrenalin. At times a slight running of the eyes and nose was observed.

Beyond a concentration effect as shown by the rise in the total number of the red cells and a rise of 10 per cent in the hemoglobin value,

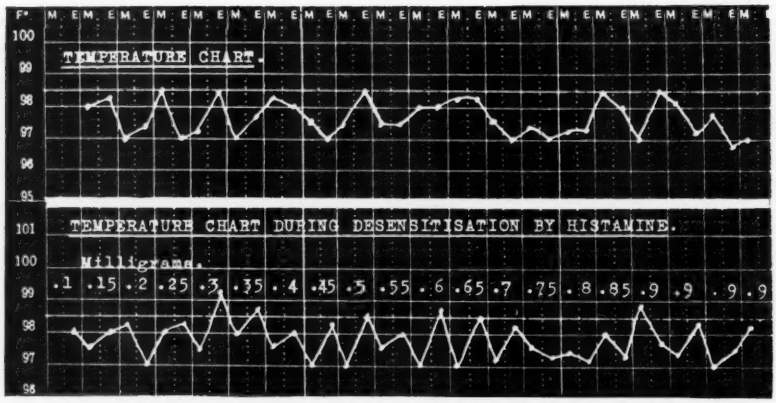
TEMPERATURE CHART.
TEMPERATURE CHART DURING DESENSITISATION BY HISTAMINE.
Milligrams.
.1 .15 .2 .25 .3 .35 .4 .45 .5 .55 .6 .65 .7 .75 .8 .85 .9 .9 .9 .9

Fig. 1.—Temperature chart before and during histamine injections.

little appreciable alteration was noted in the blood picture. The biochemistry of the blood reveals the interesting chloride shift, for while the whole blood chlorides remain practically constant there is a drop in the plasma chlorides following the injection which is balanced by the rise in the cell chlorides. There is also a drop in the urinary excretion of chloride. The blood calcium is normal.

The subnormal temperature chart was maintained both before and during the course of the injections. The patient was definitely more incontinent during the course of treatment.

The patient was discharged from hospital on August 18, three days after the last (twenty-fifth) injection of histamine. At that time placing the hand in iced water at 45° F. for five minutes was followed by a mild local urticarial reaction of the immersed part, but no lymphatic spread or general reaction was observed.

The patient revisited the Clinic on October 2, forty-five days after his discharge, during which period he had been to the seaside. In spite

of the cold weather and paddling daily, there has not been any reappearance of symptoms, and he has only wet the bed once, and then just after his return home. On repeating the immersion of the hand in the iced water for five minutes only a mild local reaction was apparent, even slighter than when he was discharged from hospital, and no lymphatic spread or general reaction followed the immersion of both hands.

PHYSICAL ALLERGY

Physical allergy is the term applied to such allergic manifestations as asthma, coryza or urticaria when brought about solely and specifically by a physical agent such as heat, cold, light or mechanical irritation, and acting either through the skin or through the mucous membranes. The reaction may appear immediately or be delayed; and may remain confined to the area which has been exposed directly to the agent (contact reaction), or spread widely and involve distant structures as well (general reaction). Patients hypersensitive to one physical agent rarely react to any other; for example, it is not usual for a case hypersensitive to cold to react to light, heat or mechanical irritation.

In regard to etiology, though the reactions are brought about solely by the application of physical agents, it is probable that each reaction within the body has some specific chemical basis. It is known that patients may be sensitized to light by the intravenous injection of hematoporphyrin, and identical effects to those of allergy to cold may be produced by the subcutaneous injection of histamine and desensitization brought about through a similar course of injections. With but one possible exception, attempts to transfer this hypersensitiveness to a normal skin have failed where the blood has been obtained from veins draining the affected area. Possibly this failure may be explained by a lymphatic spread of the liberated substance as observed in this case.

ALLERGY TO COLD

The sex incidence of the thirty-seven cases which have been reported previously shows an even distribution among males and females (Table I). In regard to age, most of the males are young adults, while the females tend toward middle life. Only one case has been reported previously during the first decade, though in many of the cases reported symptoms have been stated to have been present from early life.

Two types of case have been described. In the first, urticaria associated with hemoglobinuria appears after exposure to cold in persons giving a positive Wassermann reaction. In the second, urticaria is not associated with hemoglobinuria, a type which occurs commonly in patients with other manifestations of allergy in their present or past history or in that of their relatives, and rarely in syphilities, as in the cases reported by Mibelli and Gougerot.

The symptoms commonly have their onset after swimming, after bathing or washing in cold water, after being out in a cold wind or snow, and after eating ices or drinking cold liquids.

TABLE II. THE AGE AND SEX OF REPORTED CASES OF ALLERGY TO COLD (IN CHRONOLOGIC ORDER)

AUTHOR	M.	F.	REMARKS	REFERENCE
Behier	30+		Doctor recording his own experiences.	(Bull. Soc. méd. hôp. Paris 3: 262, 1866.)
Bourdon		45	Asthmatic.	(Bull. Soc. méd. hôp. Paris 3: 259, 1866.)
Blachez		45		(Bull. Soc. méd. hôp. Paris 9: 270, 1872.)
Negel		40	Joint pains.	(Progrès médical 12: 846, 1884.)
Schütz		25		(München. med. Wchnschr. 42: 798, 1895.)
Fraser	56			(Tr. Med.-Chir. Soc. Edinburgh 25: 90, 1905.)
Wallace		28	Asthma + coryza	(Australian Med. Gaz. 28: 436, 1909.)
Hewlett	19			(Arch. Int. Med. 11: 507, 1913.)
Netter	30			(Bull. Soc. méd. hôp. Paris 45: 339, 1921.)
Widal, Abrami and Lermoyez		37	Asthma + coryza + drug sensitiveness.	(Presse méd. 30: 189, 1922.)
Duke	43	43		(J. A. M. A. 80: 1835, 1923.)
Mibelli	15	23	Congenital syphilis.	(Gior. ital. di mal. ven. e d. pelle. 64: 673, 1923.)
Krakauer		36	Lupus erythematosus.	(Zentralbl. f. Haut-u. Geschlechtskr. 18: 754, 1926.)
Podesta	32	44	Asthma.	(Riforma med. 42: 1086, 1926.)
Watrin		11		(Bull. Soc. franç. d. derm. et syph. 34: 711, 1927.)
Gougerot, Peyre, Moutet and Bourdillon	39		Congenital syphilis.	(Bull. Soc. franç. d. derm. et syph. 34: 321, 1927.)
Joltrain, Morat and Ley	40+		Morphomaniac.	(Presse méd. 35: 1361, 1927.)
Jadassohn and Schaaf	?	?	Adult brother and sister.	(Dermat. Wchnschr. 86: 565, 1928.)
Harris, Lewis and Vaughan	64			(Heart 14: 305, 1927-1929.)
Horton and Brown	15 22 30	32 49 57		(Am. J. M. Sc. 178: 191, 1929.)
Lehner	23			(Klin. Wchnschr. 8: 306, 1929.)
Perutz, Brügel and Grünfeld	?	19		(Klin. Wchnschr. 8: 1999, 1929.)
Covisa and Prieto	2½	26		(Dermat. Wchnschr. 91: 1188, 1930.)
Haxthausen		12		("Cold in Relation to Skin Diseases." Copenhagen, 1930.)
Schmidt and Labaume		28	Urticaria pigmentosa.	(Zentralbl. f. Haut-u. Geschlechtskr. 33: 536, 1930.)
Blackford	17			(J. A. M. A. 96: 525, 1931.)

The characteristics of these reactions are: (a) the patients are very active, and so contrast with heat sensitive cases who generally seek a life of tranquillity; (b) the temperature charts are constantly subnormal and irregular; (c) the reactions are inhibited during the rise of body temperature which occurs during fevers or following exercise, and are most severe when the temperature is subnormal, as following infections and in the early morning hours; (d) some cases react most markedly after previous exposure to internal or surface heat, and (e) eosinophilia is rare.

Treatment resolves itself into the immediate alleviation of the attack, and rendering the patient insensitive to further exposures. An attack may be alleviated by the subcutaneous injection of adrenalin chloride solution, or by raising the body temperature, either locally or by plunging the hands and arms in a water-bath at 42° C., or generally by exercise or by the injection of such temperature-raising substances as B. coli vaccine.

Desensitization may be brought about by the patient's taking frequent cold baths, gradually decreasing the temperature and increasing the period of immersion (the autodesensitization of the French). It may also be accomplished by the subcutaneous injection of histamine in gradually increasing doses, as in the case recorded, or, according to French authors, by the injection of 10 c.c. to 15 c.c. of a 10 per cent solution of cesium eosinate either daily or one to three times a week. In general a dry climate is advisable in order to prevent surface cooling and so lowering the temperature of the body.

In the case reported here there are several points of interest, such as (a) the age of the patient, a boy of eight years, because only one case has been reported previously during the first decade; (b) the intense family history of allergy; (c) the history of possible previous allergic manifestations in the patient—the "gastric trouble" at two months of age, the "recurrent bronchitis" until seven years of age, the persistent enuresis to date, and the "joint pains" for the previous three months; (d) the subnormal temperature chart (Fig. 1); (e) the localization of the phenomenon to the skin, the mucous membranes remaining unresponsive; (f) the lymphatic spread of the liberated substance; (g) the prevention of the general reaction by applying a tourniquet to the forearm; and (h) the desensitization by histamine.

It has been shown that in normal persons the effect of exposure of the skin to cold depends upon its degree. According to whether the temperature is above or below 20° F. (-6° C.), a different effect is noted. Above 20° F., a single exposure leads to an immediate contraction of all the skin vessels, with the subsequent contraction of the arterioles and a dilatation of the capillaries and venules; the blood stream is slowed down, the skin temperature shows a considerable and

prolonged lowering, and the skin appears cyanotic. Below 20° F., there is an immediate solidification of the skin. Subsequently the arterioles are dilated, as well as the capillaries and venules; the blood stream is increased, the skin temperature risen considerably and the skin appears intensely red and whealed. This is the characteristic "triple response" of Lewis, and obviously 20° F. is the point of temperature at which a histamine-like substance is set free in normal individuals. In the case recorded it appears that this histamine-like substance was liberated at a temperature about 45° F., the lower the temperature below this point the more intense the reaction. This suggests that in cases showing this type of reaction to cold the threshold for the liberation of the histamine-like substance is raised some 25° F.

BOTANICAL SURVEY OF SAN JOAQUIN COUNTY IN CENTRAL CALIFORNIA

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Oakland, Calif.

THIS botanical survey of San Joaquin County includes that portion of its flora which produces or may possibly produce pollen sensitization. It was made under the direction of the writer by Prof. E. E. Stanford during 1930 and 1931. The flora of this region is similar to that of other counties along the lower Sacramento and San Joaquin Rivers.

San Joaquin County is slightly north of the center of California, being bisected by the thirty-eighth parallel of latitude. It is slightly larger than the State of Rhode Island and contains a little less than 1,000,000 acres. The western border runs into the foothills of the Coast Range and the eastern border into those of the Sierra Nevada mountains. The region, being nearly all level and subject to irrigation, produces very diversified crops. Much of the soil is alkaline in nature. Like all central California, it is very dry in the summer except for irrigated areas and ditches which flank the roads. The prevailing wind is from the northwest and, though rather constant, is rarely violent. For our purposes of study the county was divided into seven areas as indicated on the map (Fig. 1): (1) The Delta region, which has been reclaimed from tule swamps, has many levees, ditches, and canals, and its rich black soil yields perennial crops, among which asparagus and potatoes are important. (2) The Lodi section is level and subject to irrigation. Grapes, walnuts, grain, and stone fruits are the chief products. (3) The eastern range is dry, gravelly, and extends into the Sierra foothills. (4) The city of Stockton is on the San Joaquin River in the center of the county. Of the 100,000 people in the county, about 57,000 are in this city. Many types of trees line its streets and are in its parks. (5) The Tracy area is largely irrigated and much of its soil is alkaline. Alfalfa, grain, and fruits are commonly raised. (6) The Southern Range runs into the foothills of the Coast Range and is unproductive and almost unpopulated. (7) The southeastern area has much grazing and irrigated land, especially around Manteca and along the Stanislaus River.

The nomenclature as presented by W. L. Jepson, "Manual of the Flowering Plants of California," and by L. H. Bailey, "Manual of Cultivated Plants," has been used.

The flora of central California as represented by our survey of San Joaquin County differs from that of the cosmopolitan area around San Francisco Bay in several respects, as shown by my surveys of the East

Shore of San Francisco Bay,[1] of San Francisco[2] proper, and of Santa Clara and San Mateo counties. *Quercus lobata* and secondarily *Quercus douglasii* are the predominating oaks in the interior, whereas *Quercus agrifolia* is most common around the bay. The former oaks, however, are also found in Santa Clara and San Mateo counties. *Juglans hindsii*, as a cultivated tree, is extremely common in the central counties and is used for shade along streets and around homes. *Juglans regia* is extensively cultivated and is also used for shade purposes in the same dis-

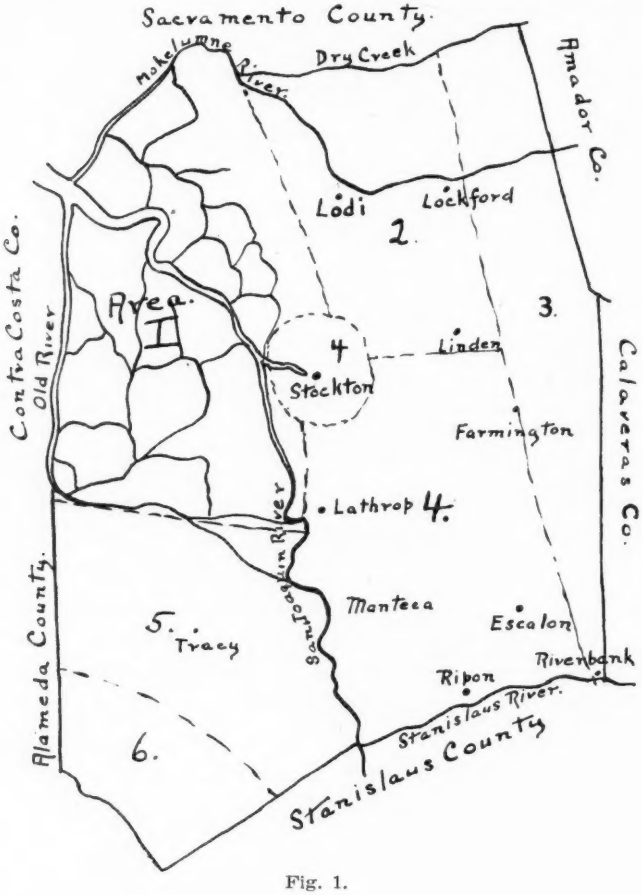

Fig. 1.

trict. *Platanus orientalis* and various species of *Salicaceae* are more common in the central area because of their growth along streams and canals. In general, the towns and many ranches have a large variety of trees which often require environmental surveys for each patient.

As compared with the bay counties the San Joaquin area, especially in the delta and in the irrigated sections has more *Amaranthaceae*, *Chenopodiaceae* (which includes *Salsola kali* and various species of *Atriplex* and *Chenopodium*) than are found in the Bay Region. The cheno-

pods, including the various species of *Atriplex,* favor alkaline soil, which is very common in San Joaquin County. *Ambrosia psilostachya* and *Xanthium canadense* are more common in the central area, whereas *Artemisia californica* and *Artemisia pycnocephala* are found only in the Bay counties. Franseria is practically absent from San Joaquin County. *Urticaceae* is more common in this area. *Holcus halepensis,* sorghum, *Echinochloa crusgalli, Festuca, Bromus, Hordeae* and especially *Distichlis* are common in the interior. In the Bay region, *Aveneae* are more frequent than in the central area and *Lolium perenne* is the chief grass to cause hay fever, as I have emphasized previously. However, my former studies have shown the importance of other spring grasses in the Bay counties.

These differences in flora are striking in view of the separation of the two areas by only fifty miles. As indicated before the Coast Range, rising to an elevation of from two to four thousand feet, separates these two regions; the interior, which has much alkaline soil and is very dry and hot in the summers, is extensively irrigated as compared to the counties along San Francisco Bay.

Patients who live in these two regions give quite different skin reactions and require entirely different antigens. Patients from San Joaquin County usually give large reactions to amaranth, chenopod, *Atriplex* and *Salsola kali* pollens, whereas reactions to the *Artemisia* pollens with or without reactions to the foregoing chenopod pollens are the rule in patients living in the Bay counties. Patients living in the Bay counties give negative or small reactions to *Cynodon dactylon* as compared with the frequent large reactions to this pollen in patients from the interior county.

The special environmental flora of each patient moreover in regard to trees, shrubs, flowers, and the predominating flora, as shown in my survey, must be considered. This emphasizes the necessity of the preparation of individual antigens after thoroughly testing the patient with all common pollens to which he is exposed, as determined by the flora of his vicinity; also the study of his environmental surroundings, and, at times, the study of pollen plates from his own district.

It is my growing conviction that all types of pollens as well as spores must be considered as possible causes of allergy in the etiology of hay fever, asthma, bronchitis, dermatitis, and of pollen toxemia. This necessitates the study of the trees, shrubs, grasses, weeds, and flowers which are in the patient's neighborhood and immediate environment, even though they produce little pollen and largely depend on insects for pollination. Many of the so-called insect pollinated trees and flowers, such as acacia, rose, chrysanthemum, aster, dahlia, and dandelion, have produced severe symptoms in my patients which have necessitated specific pollen therapy. Pollens of the many types of fruits which are

NAME		HABITAT OR USE	DURATION*												DISTRIBUTION BY DISTRICTS‡						
SCIENTIFIC NAME	COMMON NAME		JAN.	FEB.	MAR.	APR.	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	D.	L.	E.R.	S.	T.	S.R.	S.E.
Group 1. Trees and Shrubs																					
Aceraceae	Maple Family	Stream bottoms; occasionally planted for shade																			
Acer Negundo var. californicum	Box elder			1	1111	1										2		1			2
Acer saccharinum	Silver Maple	Street tree		111	11											3		3	2		1
Anacardiaceae	Cashew Family	Roadsides and uncultivated soil				1111	1111	1111	1111							2	1				
Rhus diversiloba	Poison Oak																				
Schinus molle	California Pepper Tree	Street and ranch tree						11	1111							2		2	1		1
Betulaceae	Birch Family																				
Betula alba laciniata pendula	Weeping birch	Street tree; parks, lawns														1		1			1
Caprifoliaceae	Honeysuckle Family	River bottoms, waste places				1111	11									1		1			1
Sambucus glauca	Blue elderberry																				
Celastraceae	Staff-tree Family																				
Evonymus japonica	Japanese Evonymus	Park and lawn shrub						111	1111							3		3	1		
Cupressaceae	Cypress Family																				
Chamaecyparis lawsoniana	Lawson Cypress	Parks and lawns					111									2		2	1		1
Cupressus spp.	Cypress	Parks, lawns, cemeteries, roadsides				111	1111									1		1	1		1
Juniperus spp.	Juniper	Parks and lawns														1		1			1
Thuja orientalis and other spp.	Arbor Vitae	Parks and lawns				1111	11									2		2			1
Fagaceae	Oak Family																				
Castanea sativa and hybrids	Chestnut	Ranches and orchards					111	11								1					1
†*Quercus douglasii*	Blue Oak	Open hilly country			11	11										2	3			2	1

†*Quercus douglasii*	Blue Oak	Open hilly country			11	11											2	3			2	1

†*Quercus lobata*	Valley Oak	Open land			11	111										1	3	3	1	1	2	3
Quercus wislizeni	Interior Live Oak	Open hilly country and riversides			1	111											2	2				1
Juglandaceae	Walnut Family																					
†*Juglans hindsii*	California Black Walnut	Roadsides, ranches, grafting stock, etc.				1111										1	4	1	2	3		3
†*Juglans regia*	English Walnut	Orchards, roadsides, ranches, etc.				111	11									1	4	1	3	2		3
Leguminosae	Pea Family																					
Acacia spp., chiefly A. melanoxylon	Acacia, Wattle	Streets and roadsides, ranches		1	1111	111											3		4	3		2
Robinia pseudacacia	Locust	Roads, streets, ranches				11	1111										1		1	1		
Meliaceae	Mahogany Family																					
Melia Azedarach	Umbrella Tree	Streets, parks, ranches					111										3		3	1		1
Moraceae	Mulberry Family	Streets, ranches				111	11												2			1
Morus spp.	Mulberries	Climbers over porches, crop					11	1111									1	1	1	1	1	1
Humulus	Hop																					
Toxylon pomiferum	Osage Orange	Road hedge					11	11									1					1
Myrtaceae	Myrtle Family																					
Eucalyptus spp.	Blue Gum, Ironbark, etc.	Roadsides, streets, parks, ranches, etc.		11	1111	1111	1111	1111								1	3	1	2	3		3
Myrtus communis	Myrtle	Shrubs around houses					11	1111	1111	1111	11						2		3	1		1
Oleaceae	Olive Family																					
Forsythia spp.	Forsythia	Shrubs around houses			111														1			
Fraxinus oregona	Oregon Ash	Along streams		11	1111												2					2
Fraxinus velutina	Arizona Ash	Street and roadside tree		1111													1		3			1

*Each figure "1" represents approximately one week.

‡Numbers indicate relative amount in each district: 1, rare; 2, occasional; 3, common; 4, abundant. D., Delta; L., Lodi; E.R., Eastern Range; S., Stockton; T., Tracy; S.R., Southern Range; S.E., Southeastern.

†The most important hay fever producing pollens.

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Group 1. (Cont.) Trees and Shrubs																					
†*Ligustrum spp.*	Privets	Hedges chiefly						1111	1111							3		3	2		2
†*Olea europaea*	Olive	Orchard crop; streets, roadsides, ranches					1111	11								3	1	2	1		3
Palmaceae	Palm Family																				
Chamaerops humilis	Dwarf Palm; European Fan Palm	Parks, lawns, streets				1111										1		2			1
Phoenix dactylifera	Date Palm	Parks, streets														1		1			1
Phoenix canariensis	Canary Island Palm	Parks, streets, house lots roadsides														3		3	2		2
Trachycarpus excelsa	Japanese Windmill Palm	Parks, streets				1111										1		1			
Washingtonia filifera and varieties	California Fan Palm	Parks, streets, house lots roadsides														3		3	2		2
Pinaceae	Pine Family																				
Abies spp.	Firs	Parks, house lots														1		1	1		1
Cedrus deodara and other spp.	Cedars	Parks, house lots									11	1111				2		3			1
Picea spp.	Spruce	Parks				1111	1											1			1
Pinus spp.	Pines	Parks, roadsides			1111	1111	1111									1		1			
Platanaceae	Sycamore Family																				
†*Platanus orientalis*	London or "oriental" Sycamore	Streets, roadsides			11	11									1	3		4	3		2
Platanus occidentalis	American Sycamore				11	11												1			

Salicaceae *Populus balsamifera and other spp.*	Willow Family Cottonwood	Roads, streets, windbreaks		1	1111	1											3		3	2		2
Populus fremontii	Fremont Cottonwood	Along streams		11	111												2		1	1		2
Salix babylonica and other weeping spp.	Weeping Willow	Around streams and wet places, parks, etc.		1	1111	1										3	1		1		1	1
Salix laevigata	Red Willow	Along streams			1111	11										2	2	1	1			2
Salix lasiolepis	Arroyo Willow	Along streams		111	11											4	2	1	1	1	1	3
Salix nigra var. vallicola	Black Willow	Along streams, irrigating ditches			1111	11										3	2	1	1	2	1	3
Salix sessilifolia var. hindsiana	Sandbar Willow	Along streams and wet places in sandy soil			1111	1111	1									2	3		2	3		3
Simaroubaceae *Ailanthus altissima*	Quassia Family Chinese Sumac	Roadsides, streets, ranches					1111										2		2			2
Tiliaceae *Tilia spp.*	Linden Family Linden	Street tree					111												1			
Ulmaceae †*Ulmus procera and varieties and other spp.*	Elm Family Elm	Streets, roads, parks, ranches	1	1111	1											1	3	1	4	3	1	3
Vitaceae *Vitis vinifera, etc.*	Grape Family Grape	Vineyards, ranches, gar lens, back yards				1111	11									1	4	2	3	2		3
Group 2. **Herbaceous Plants** A. DICOTYLEDONS																						
Amaranthaceae *Amaranthus blitoides*	Amaranth Family Prostrate Pigweed	River bottoms, gardens					1111	1111	1111	1111	1111								1			
†*Amaranthus graecizans*	Tumbleweed	Roadsides, gardens, etc.					11	1111	1111	1111	1111					4	4	2	4	4	1	4

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Group 2. (Cont.) Herbaceous Plants																					
A. DICOTYLEDONS (Cont.)																					
Amaranthus hybridus	Pigweed	Weed of cultivation					111	1111	1111	1111	1111				3	3	1	3	2	1	3
†*Amaranthus retroflexus*	Rough Pigweed	Weed of cultivation					111	1111	1111	1111	1111	11			4	4	2	4	2	2	4
Chenopodiaceae	Goosefoot Family																				
Atriplex argentea var. expansa	Fog-weed	Alkaline soil, grain fields						1	1111	1111	1111				2	1		2	3	1	2
Atriplex decumbens		Alkaline soil, borders of irrigating ditches						11	1111	1111	11				2	3		2	2		3
Atriplex hastata	Fat-Hen						11	1111	1111	1111	1111	1			1	1		1	3	1	
Atriplex phyllostegia	Watson Arrow Scales	Alkaline soil, vacant lots waste places					1	1111	1111	111					1	1		1			
†*Atriplex rosea*	Salt Bush	Alkaline soil, vacant lots, waste places							11	1111	1111	1111			3	1		2	3	1	2
Atriplex semibaccata	Australian Salt Bush	Waste alkaline marshes					1	1111	1111	11					1	1					
Beta vulgaris	Sugar Beet	Crop							1111	1111	111				4	1			3		3
†*Chenopodium album*	White Pigweed Lamb's-quarters	Alkaline soil, weed of cultivation			1	1111	1111	1111	1111	1111	1111	1			2	2	1	2	3	2	2
Chenopodium ambrosioides	Mexican Tea	Levees, waste places								1111	1111				3	1	1	1	1	1	
†*Chenopodium anthelminticum*	Wormseed	Levees, waste places, roadsides, back yards		11	1111	1111	1111	1111	1111	1111	1111	1111	11		3	2	1	3	2	1	2
Chenopodium botrys	Jerusalem Oak	River bottoms, gardens						1111	1111	1111	1111	1111			3	1	1	1	1	1	1
Chenopodium murale	Sowbane; Nettleleafed Goosefoot	Weed of gardens and waste places in broken soil		1111	1111	1111	1111	1111	1111	1111	1111	1111	111		2	3	1	3	3	1	3

Kochia scoparia var. trichophila	Summer Cypress	Cultivated around houses							1111	1111	1111	1111	11				2		2			
Nitrophila occidentalis		Very alkaline soil					111	1111	1111	1111					1	1	1	1	1	1	1
†*Salsola kali var. tenuifolia*	Russian Thistle	Alkaline sand, roadsides grain fields					1	1111	1111	1111					1	1	1	1	2		2
Spinacea oleracea	Spinach	Crop				1111															2
Suaeda moquini	Alkali Blite	Very alkaline soil			1111	1111	1111	1111	1111										1		1
Compositae †*Ambrosia psilostachya*	Composite Family Western Ragweed	Roadsides, waste places						1111	1111	1111	1111	1111	11	2	2		2	2			2
Artemisia biennis		Ditches, river bottoms, moist soil						1111	1111	1111	11			1	1			1			
†*Artemisia vulgaris (var.)*	Mugwort	Ditches, river bottoms, moist soil						1111	1111	1111	11			3	3	1	3	3	3		2
Franseria acanthicarpa	False Ragweed	Roadsides, waste places						11	1111	1111	1				2						
Iva axillaris	Poverty Weed	Cultivated areas						1111	1111	111				2							
†*Xanthium canadense*	Cocklebur	Sandy soil, river bottoms, waste places						11	1111	1111				2	2	1	1	2	1		2
Xanthium spinosum	Spiny Clotbur	Waste places, barnyards, roadsides					111	1111	1111	1111				2	2	1	1	2	1		2
Anthemideae Artemisia vulgaris vars.	Mayweed Tribe Mugwort	River sides, levees, roadsides, waste places					1	1111	1111	1111	1111			3	2	1	2	2	1		2
Astereae Solidago occidentalis	Aster Tribe Western Goldenrod	River bottoms, moist waste places							1111	1111				1	1		1		1		1
Euphorbiaceae Eremocarpus setigerus	Spurge Family Turkey Mullein	Roadsides, grain fields					11	1111	1111	111					1		1				2
Ricinus communis	Castor Bean	Flower gardens, etc.						11	1111	1111	111				1		1				
Heliantheae Helianthus annuus	Sunflower Family Common Sunflower	7000 acres cultivated						11	1111	11					1		1	1			1

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Group 2. (Cont.) Herbaceous Plants																					
A. DICOTYLEDONS (Cont.)																					
Plantaginaceae	Plantain Family	Dry range country			11	1111	11										3			1	3
Plantago erecta	Small Plantain																				
†*Plantago lanceolata*	Ribwort	Lawns, irrigated soil, river bottoms				11	1111	1111	1111	1111	1111	11			1	2		2	2	1	1
Plantago major	Plantain	Lawns, river bottoms				11	1111	1111	1111	1111	1111				2	1	1	1	2	1	
Polygonaceae	Polygonum Family	Roadsides, moist, wet places			111	1111	1111	111							3	3	2	3	2	1	2
†*Rumex crispus*	Curled Dock																				
Rumex pulcher	Fiddle Dock	Roadsides, river bottoms				111	1111	1111	1111						1	2	1	1	1	1	2
Urticaceae	Nettle Family	Levees, roadsides, etc.					1111	1111	1111	1111					4	2		1	1	1	2
Urtica gracilis vars.	Creek Nettle																				
Urtica urens	Small Nettle	Waste places			1	1111	1111											1			1
Group 2. B. Monocotyledons																					
Cyperaceae	Sedge Family	River banks, waste places				111	1111	1111							1	1		1			1
Carex spp.	Sedges																				
Cyperus spp.	Galingales	River bottoms, along irrigating ditches, etc.				111	1111	1111	1111	1111	1111				3	2		2	1		2
Eleocharis spp.	Spike Rush	Wet places by roadsides, etc.				1111	1111									2	1	1			
Scirpus acutus	Tule	In edge of slow streams irrigating ditches, etc.				11	1111	1111	1111						4	2	1	1	1	1	2
Gramineae	Grass Family															1	1	1		1	1
Agrostideae	Timothy Tribe																				

Agrostis palustris	Redtop	Lawns and golf courses				11	1111	11										1		1			
Alopecurus saccatus	Meadow Foxtail	Wet places				1111																	
Polypogon lutosus	Beard Grass	Wet places					111	1111	1111											1			1
Polypogon monspeliensis	Beard Grass	Along irrigating ditches wet places, gardens, etc.					111	1111	1111						4	3	1	2	2		2
Andropogoneae †*Holcus halepensis*	Sorghum Tribe Johnson Grass	Waste places							11	1111	1111				2	2	1	2	2	1	2
†*Holcus sorghum*	Sorghum	Field crop							111	1111					2	2			2		2
Aveneae *Aira danthonioides*	Oat Tribe Hair Grass	Moist places			11	1111	11								1	1	2	1	1	1	2
Avena barbata	Slender Wild Oat	Sandy and gravelly soil		11	1111	1									1	1	2		1	3	2
†*Avena fatua*	Wild Oat	Uncultivated soil		11	1111	111									1	4	3	3	3	3	4
Avena sativa	Oat	Field crop				11	111								2	3	2	2	2	1	3
Chlorideae †*Cynodon dactylon*	Grama Tribe Bermuda Grass	Lawns, parks, roadsides, alkaline soil				11	1111	1111	1111	1111	1111	111			2	2	1	3	2	1	2
Festuceae *Briza minor*	Festuca Tribe Quaking Grass	Range				1111	11										3				
†*Bromus hordeaceus*	Soft Cheat	Uncultivated soil			111	1111	11								3	4	4	4	4	3	4
†*Bromus rigidus*	Broncho Grass	Roadsides, range, waste places			11	1111	11								3	4	4	4	3	2	4
Bromus rubens	Foxtail Brome	Waste places in sand and gravel				1111	11								1	2	3	2	3	3	3
Bromus racemosus	Smooth Cheat	Range country				1111	11										2				2
Bromus unioloides	Rescue Grass	Weed					1111											1			
Cortaderia argentea	Pampas Grass	Ornamental; parks, lawns																1			

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Group 2. (Cont.) **B. Monocotyledons**																					
†*Distichlis spicata*	Salt Grass	Alkaline soil in waste places				1111	1111	1111	1111	1111					2	2		2	3		
Eragrostis orcuttiana		Weed of cultivation							1111	1111	1111							2			
Festuca confusa		Range				1111											2			2	
†*Festuca megalura*		Waste land, range			11	1111	11								2	4	4	3	3	3	4
†*Festuca pacifica*		Range, waste land			11	1111	11								2	4	4	4	4	4	4
Festuca spp.	Meadow Fescue, etc.	Lawns, parks, etc.	Rarely flower except in neglected lawns													2		2			
Melica imperfecta		Range				1111														1	
Pleuropogon californicus		Ditches				1111										1					
Phragmites communis	Reed	Levees, river sides							1111	1111					3						
†*Poa annua*	Annual Blue Grass	Lawn weed, range in wet places		11	1111	1111	1111	1111	1111	1111	1111	11			1	3	3	3	3	2	3
†*Poa pratensis*	Kentucky Blue Grass	Lawns, parks				1111	1111	1111	1111	1111					1	3	1	3	2	1	2
Hordeae †*Elymus triticoides*	Barley Tribe Rye Grass	Roadsides, alkaline soil					11	1111	1111						3	3	2	3	3		2
†*Hordeum gussoneanum*	Alkali Barley	Range, alkaline soil, waste places			11	1111	1								3	4	4	4	4	4	4
†*Hordeum murinum*	Wall Barley	Roadsides, wet places, common weed			11	1111	11								2	4	3	4	4	3	4

Hordeum nodosum	Meadow Barley	Wet places			11	1111	111										2					
†*Hordeum sativum*	Barley	Field crop			111	1111	111									4	4	2	1	4	3	4
Lolium multiflorum	Italian Rye Grass	Roadsides and waste and damp places				1111	1111	1111								1	2	1	2	1	1	1
†*Lolium perenne*	English Rye Grass	Roadsides, damp places				11	1111	1111	11							1	3	1	3	2	1	2
Lolium temulentum	Darnel	Roadsides, damp places				1111	1111										1		1	1		1
Secale cereals	Rye	Field crop, sand binder					1111													1		1
Triticum sativum	Wheat	Field crop					1111	11								4	4	1	1	3		4
Maydeae *Zea mays*	Maize Tribe Indian Corn	Field crop						11	1111	1111						4	2		1	3		3
Paniceae *Chaetochloa lutescens*	Millet Tribe Yellow Foxtail	Garden weed							111	111									1			
†*Echinochloa crus gal and var. zelayensis*	Water Grass Barn Grass	Weed of cultivation and wet places						11	1111	1111	1					4	3		2	3		3
Paspalum distichum	Joint Grass	River bottoms and irrigating ditches							11	1111	1111						2		2			2
Phalarideae *Phalaris arundinacea*	Canary Grass Tribe Reed Canary Grass	Near water					111	111								1			1	1		1
Phalaris Lemmonii		Wet places				1111										1	2	1	2	1		2
Phalaris minor	Canary Grass	Roadsides, etc.				11	1111										3		2			2
Juncaceae *Juncus balticus, etc.*	Rush Family Bulrushes	Wet places				1111	1111	1111								3	2	1	2	1		1
Liliaceae *Asparagus officinalis*	Lily Family Asparagus	Field crop						1111	1111							4	2					
Typhaceae *Typha latifolia*	Cat-tail Family Cat-tail	Wet places					111									4	2		2	1		1

cultivated extensively produce sensitization in certain patients who live in the orchard districts. Proximity to this type of flora is the important consideration which in turn necessitates environmental study. Pollen plates are obviously important.

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ASTHMA DUE TO A MOLD*

Hypersensitivity Due to *Cladosporium fulvum*, Cooke. A Case Report

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IN THE study of allergic conditions, diagnosis is extremely difficult in cases where the usual offending atopens give no reactions. It must be borne in mind that any single, simple or combined protein may become at any moment the stimulating agent which excites specific allergic manifestations. In fact, not all allergic conditions are due to protein sensitivity alone; Urbach,[1] has shown that sensitivity may be due to carbohydrates or ether soluble fats in oils. The work of Parlato,[2] with emanations from flies and of Cobe,[3] with emanations from Christmas trees, demonstrates that not infrequently common but unsuspected sources may be atopic. This is particularly true of seasonal stimulants.

The importance of a careful history has been stressed time and time again. The information which may be elicited before definite tests have been made often gives a logical clue to the possible offender. Patients themselves generally have knowledge of substances which aggravate allergic conditions, and these substances, no matter how remote they may seem, are not to be disregarded but should be eliminated only through definite skin tests. Grooms who give a typical history of "horse dander asthma" recognize the cause as being due to horses long before they come to a physician for relief.

Molds have become recognized offenders as atopens in bronchial asthma. Cadham[4] in Canada and Hansen[5] in Heidelberg have published material showing skin reactivity to molds. In America, Hopkins, Benham and Kesten[6] and Bernton[7] have been the pioneers. We have suspected that the chief offenders in house dust extracts were molds, and we have a series of unpublished cases with cutaneous reactions to the molds isolated from the house dust.

Through the courtesy of Dr. U. Grant Gifford of Kennett Square, Pa., I had the opportunity to see the following case which we believe should be placed on record because of its unusual atopen and the corresponding success in desensitization:

CASE REPORT

The patient has been a worker in a greenhouse where tomatoes are cultivated. He has owned and worked the same place for several years. Physically he was very emaciated, also crippled due to a fall some years previously. When first seen he was acutely ill with violent asthmatic

*From the Wilmer Research Foundation in the Laboratory of the Germantown Hospital, Philadelphia.

attacks. He had constant and pronounced lachrymation, very profuse watery discharge from the nose and typical difficulty in breathing. Accompanying these was a persistent cough, paroxysmal in type. The discharge from the nose was several ounces per day and the cough very productive. Sleep was impossible and hypodermics of adrenalin three to five times nightly gave but mild relief. Some pleural friction rubs could be heard over the upper right chest anteriorly and some inspiratory râles in the same region but without impaired resonance or prolongation of the audibility of expiration. Sputum examinations were all negative for tubercle bacilli. When the history was taken, the patient stated that he was free from asthma most of the year and only developed these severe attacks after a mold had appeared on the leaves of the tomato plants under cultivation. This lasted in increasing severity until the plants were taken up the latter part of August, and two weeks after the last of the plants were uprooted he was asthma free until the following June.

The patient was skin tested routinely with all of the common seasonal pollens and all tests were negative. A few leaves of the infected tomato plants were brought from the greenhouse to the laboratory and examined. The leaves had a grayish brown mold on them. This was scraped off carefully and plated on Sabouraud's maltose agar media. Growth was profuse and easy. Some of the mold was then reinoculated into maltose broth in a 500 c.c. flask and allowed to grow until a flat, feltlike mat had covered the entire surface of the broth. This felt is a mat of the hyphae and the conidiophores of the mold. A culture of the mold was sent to Dr. Chas. Thom, Mycologist of the United States Department of Agriculture, who identified it as *Cladosporium fulvum*, Cooke.

The feltlike mat of mold was then powdered and extracted. Some of the leaves of the tomato plants which had been freed of the mold by scraping and washing were also extracted. This testing material was prepared by extraction with a 12 per cent alcoholic normal saline fluid at room temperature, made sterile by filtration through a Berkefeld candle and preserved with a 1 per cent merthiolate (Lilly) solution. Skin tests were made by the scratch method with the special extracts and were controlled with other extracts of stock molds prepared similarly.

RESULTS OF SKIN TESTS

Control (extracting fluid)	negative.
Tomato leaf extract	negative.
Cladosporium fulvum	4 plus.
Aspergillus niger	negative.
Aspergillus fumigatus	negative.

The patient was treated with an extract prepared similarly to the testing material, and the result of treatment was outstandingly success-

ful. The patient was advised to move temporarily a few miles from the greenhouse so as to avoid atmospheric contact with it. While away he received an injection of 0.2 c.c. of the extract and a second dose of 0.4 c.c. four days later. These were followed with such marked relief that against the advice of his physician he moved back into his home and greenhouse. In spite of this, improvement has been constant. The eyes and nose are normal, bronchial râles are practically gone, and in the patient's own words, "I expectorate about one-fortieth as much as formerly." While continuing his schedule of treatment the plants were removed from the greenhouse with a great deal of dissemination of the mold. The patient regards this as the greatest possible exposure. In previous years this was an extremely dreaded and severe experience for him. This time it was attended with very little discomfort; no trouble with the eyes or nose and only a slight bronchial difficulty.

DISCUSSION

This case presents three striking features: one is the specificity of the reaction of the mold, all of the freshly prepared cultures of stock molds being negative. Another is the rarity of the atopen, and the third the rapidity of relief through desensitization. A search of the literature, by both Dr. Thom and myself, shows no record which involves this mold in allergic diseases. Since this case, Bernton[8] has identified *Cladosporium* in a case of a young child. F. L. Wellman,[9] of the United States Bureau of Plant Industry, describes the organisms causing this disease in tomato plants as "a fungus which has dark colored hyphae and conidia. The conidia are easily detached from the conidiophores and are disseminated by wind currents or on the clothes and hands, etc., of the gardeners. Leaf lesions are covered with a powdery mat of gray conidia, from which the disease gets its name."

SUMMARY

A case is reported of a patient susceptible to a mold, (*Cladosporium fulvum*, Cooke), appearing on the leaves of tomato plants.

Marked improvement and relief occurred through desensitization with extract made from the mold infecting the tomato plants.

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THE IMPORTANCE OF MEDICAL SOCIAL SERVICE IN ASTHMA CLINICS*

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THE idea of the social service originated in England where the first work was in great measure an effort to discourage the abuse of the hospital facilities intended for the poor.[1] To this original conception of protecting and furthering the interest of the institution and its physicians, gradually was added that of the duty of the hospital toward its patients, so that in time the activities of the social service became indispensable in the intelligent treating of clinic patients, supplying the point of personal contact so necessary and otherwise so lacking.

The nature of bronchial asthma prevents, to a large extent, any type of group treatment or standardization of therapy, since each patient presents an individual problem, due largely to the diversity of possible etiologic factors. The investigation of such factors requires a painstaking study of the patient's environment at home and at work, since usually the excitants of the asthmatic condition are derived from these sources. It will thus be seen that for proper diagnosis and treatment the study of each patient must extend beyond the walls of the hospital. Such extramural duties naturally fall to the lot of the social service worker, who must, however, be properly trained in this phase of the work.

Among the very earliest, if not the earliest, of organizations to recognize the need for such social service cooperation was the Clinic of Applied Immunology at the New York Hospital, under the direction of Dr. Robert A. Cooke, where more than ten years ago such a procedure was established. The method to be described, based upon the New York Hospital idea, has been in use at the Hay Fever and Asthma Clinic of the Post-Graduate Hospital for the past six years.

Upon application to the Asthma Clinic for treatment, each patient is first interviewed by the social service worker who explains the nature and scope of the treatment and inquires as to the financial qualifications for admission. If such qualifications appear questionable, the patient is admitted for treatment until proper investigation by the worker can be made.

No inspection is made of the home of the patient until after the fourth dispensary visit, by which time the study as to the cause of the asthmatic condition has been completed and the social service worker is furnished with a list of the suspected exciting factors. These factors

*From the Clinic of Applied Immunology, Department of Medicine, N. Y. Post-Graduate Medical School and Hospital, Columbia University.

are determined by the intracutaneous tests with the extracts of the various airborne inhalant substances, and foods. Among the more important of these factors are: pollens; dusts; animal emanations, such as dog, cat, horse, rabbit, goat, chicken, duck and goose epithelia; orris; rice powder; pyrethrum; silk; flax; cotton; and wool. It will be readily seen that the patient comes in contact with many of these substances in the form of bedding, clothing, home furnishings and work shop materials. With the list of suspected irritants at hand the worker visits the home, searches for the factors involved and suggests their removal. This procedure is quite incomprehensible to many dispensary patients, requiring tact and patient explanation on the part of the worker. The bedding must receive particular attention, since this is frequently the source of irritation, not only feathers but goat hair, rabbit hair, cotton, kapok and grass being employed in pillows and mattresses. The type of floor covering and bedding, the presence of stuffed toys or of pet animals, the use of insect powders, or sprays, the state of cleanliness of the dwelling, its floor level, its type of heating, its proximity to stables, shops or factories with irritating fumes, must all be considered.

In the patient with an occupational type of asthma it may be necessary to visit the shop, factory or bakery in which he works. Wherever possible a sample of any material suspected as causing discomfort to the patient is obtained and brought to the physician in the clinic for inspection and analysis.

While at the patient's home the social service worker explains any general or dietary measure which may have been advocated by the physician. The worker after making this visit reports to the physician in charge, and submits a written record of her findings, upon the form illustrated, which is attached to the patient's history. Any suggestions made to the patient by the worker are also included on the report.

With the information thus procured the physician is no longer in doubt as to the significance of many of the findings by cutaneous test. For instance, a positive test to rabbit epithelium is of doubtful value unless the worker has detected rabbit hair in the furnishings, the mattresses, pillows or cushions in the home, or among the materials used in the shop. With such findings by test, verified by the presence of these irritants in the environment, their significance is greatly enhanced, and the problem of diagnosis is clarified. Furthermore, just as the detection of such an irritant as the rabbit hair is important in the diagnosis, just so is its removal important in treatment, since no schedule of hyposensitizing injections can be expected to be successful as long as the excitant remains in the patient's environment. For this reason, subsequent to the first visit, the patient is again interviewed by the worker, in order to ascertain whether the suggested changes have been made and often a second home visit is made.

ASTHMA CLINIC—SOCIAL HISTORY

NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL

DEPARTMENT OF IMMUNOLOGY

Name Address Fl.

Date Clinic No. Phone No. Ins.

Age Sex Color Rel. M. S. W. Citizen

Sanitary Condition of Street Type of Building—Rent

No. of Rooms	Ventilation	Dampness	Stove	Toilet
No. of light			Steam	Sink
No. of dark			Gas	Bath

Occupation History

Household

Name	Kinship	Age	Nativity	Yrs. in U. S.	Occupation	Average earnings	Phys. Mental Condition

Sanitary Condition of Rooms

Pets:	Bedding:	Insecticides:	Floors:	Walls:
Cat	Hair Feathers	CN Flytox	Carpet	Paint
Dog	Cotton	Eureka Black Flag	Oilcloth	Paper
Bird	Silk Floss	Flit	Bare	

Remarks:

In the asthma clinic at the Post-Graduate Hospital, inspection and check-up visits to the home or the shop by the social service worker numbered 470 in 1931 and 512 in 1930, every case residing within the metropolitan area being visited. Many puzzling and unusual problems were solved as a result of these visits. In one patient, asthmatic attacks, continuing after all recognized sources of the irritant, cottonseed, were removed, were found to be due to this substance used as stuffing in his daughter's doll. Another patient, a boy, who developed asthma only when working in his father's fruit shop was negative to all tests, but was found to be clinically sensitive to the insecticide sprayed about the place,

to drive flies away. In another case, that of a girl working in a beauty parlor, who was flaxseed sensitive, the excitant was found to be contained in a hair wave lotion with which she came in daily contact.

So valuable has become the information obtained by such visits that in the study of the hypersensitive case this procedure is regarded as next in importance to the intracutaneous testing; for, regardless of the factors found positive by test, they remain of doubtful importance until their clinical significance has been established for each patient. The reaction to flaxseed, for instance, found positive in the young girl working in the beauty parlor, would have meant little unless it had been established by investigation that there was constant contact with this excitant.

In addition to the activities here described for which the workers must be especially trained, the usual follow-up system is maintained. Former patients are requested to report by letter or in person, every six months, for the first year following the conclusion of treatments. When indicated, reexamination and, if necessary, resumption of treatment are instituted. By this procedure the patients in general are kept in better health, and the records of the clinic become more comprehensive.

As a natural result of these contacts in the home and in the clinic the social service worker becomes to the asthmatic patient, so often disheartened, the personal representative of the dispensary service to whom he can turn for advice and cooperation. This idea of personal and sympathetic contact between the patient and the social service worker has been encouraged, since a successful result in treatment can come only through a thorough understanding of the problems met in the daily routine of the asthmatic patient, whether in dispensary or private practice.

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CLIMATIC ASTHMAS*

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THE influence of climate on asthmatics is not doubted, not only in cases where no other definite cause is recognizable but in all cases in general. We already know that in the causal complex of an attack of asthma, the presence of allergens is not the only factor. On the contrary, as we have mentioned in former studies, other causes coincide, preparing the ground and giving their special characteristics to asthmatics. There are times when the reaction appears diminished, and we may speak of a balanced allergic state.[2, 3, 4] However, there exist other conditions, even when the quantities of allergens in the environment are equal, which act in such a way as to give us a more satisfactory answer. We have already ascertained this in regard to different periods of the year, in relation to the acid base equilibrium,[5] in keeping with the estrual cycle, and so on. It may be possible that different climatic conditions act in such a manner as to vary the usual results of etiologic agents. This is not to be wondered at if we remember that the patient is subject to changes in vegetation corresponding to the climate to which he is subjected, and also to changes in weather. There are facts which demonstrate the effect of climate on asthmatics, the attacks in question are not caused by the climate alone. We shall give a summary of these later. More interesting, by far, however, is the fact that there are cases of asthma in which one can ascertain no other cause apart from climatic influence, and these we may truly call climatic asthmas.

We owe our knowledge of the working of climatic influence principally to independent and simultaneous researches of Van Leeuwen and of Leopold and Leopold. Van Leeuwen made a special study of the occurrence of asthma in Holland, showing by a chart the incidence in each region and thus proving that there are certain localities especially favorable to asthma and others in which it rarely appears. The former regions invariably are humid and marshy places with fertile soil, while the latter consist of drier inland localities. The constancy of this comparison led the author to believe in the existence of some element in the atmosphere which is conducive to asthma. Extracting some air, and making several cutaneous experiments with it on asthmatics, he was able to prove that with air from asthmogenic places one could provoke much stronger reactions than with air from higher regions (different parts of Switzerland), where most patients remain free from attacks. Therefore, it seemed clearly proved that asthmatics were likewise cases of allergy, and that climatic influence was not directly due to temperature, humid-

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ity, etc., but to the abundance in the air of certain substances, allergenic or climatic miasma, to which some people are particularly susceptible. The most convincing proof was obtained on finding that in rooms in which the air entering was perfectly filtered and purified[6] asthmatics remained free from attacks. The therapeutic effect of these rooms which were free from allergens has been proved in later years by various workers. At the same time, Leopold and Leopold[7] with a fundamentally different apparatus but with the same object in view gave a similar demonstration. The majority of asthmatics in Holland appear to have attacks from climatic and house allergens, so the number of cases obtaining relief from the aforesaid apparatus was really great.

What is the nature of these allergens in the ambient air? Van Leeuwen, Bien, Kremer, and Varekamp[8] considered that fungi producing tiny spores might be the cause. They demonstrated this by cutaneous reactions with extracts of aspergillus, which proved positive in 40 per cent of the cases under observation. Many of these cases were in reality the kind we might refer to as "bed asthmas," i. e., those with constant nocturnal attacks, and sensitivity to bedding (feathers, eiderdown, mattresses, etc.), which suggests and in some cases directly proves that a parasitic fungus in these articles acts as a source of allergens. Nevertheless, many of these cases may be climatic asthmas in the strict sense of the phrase.

Though as previously stated, climate influences nearly all asthmatics, yet climatic cases exclusively are not so frequent in Spain, doubtless because of the composition of the soil. At present, only 17 of the 292 cases in our last available statistics appear as climatic asthmas.[9] Therefore, and this is very important, of the above 17 cases 14 were patients from a village on the coast and the remaining three came from humid localities. Wherefore, acknowledging that in the greater number of asthmatics the influence of climate is clearly perceived, we believe that almost all cases of pure climatic asthma are exclusively seaside cases. They all improve and remain free from attacks on moving inland, and generally one may clearly perceive by their history the influence of maritime climate. From the above consideration, climatic asthma and seaside asthma seem to us synonymous terms. In several cases under observation this has been very evident. Attacks invariably disappear when the patient goes inland and reappear in the proximity of the sea. The determining factor in the appearance of attacks is not always so clearly seen. There are times when these seem to obscure the cause of climatic asthma. In our opinion the principal reason for this is as follows. Fungi naturally accumulate in dust and furniture, where capacity for accumulation is great. Therefore, when the medium on which it falls is propitious, it increases abundantly, constituting a veritable focus of reproduction. Thus we often observe that a patient suffering from what is thought to be climatic asthma is usually only attacked in one particular house, al-

though he may suffer from occasional attacks in another residence under similar conditions. This also explains why similar patients have attacks in nearby inland places, though not in distant seaside resorts; since some object belonging to them, freely infected with the germs, may have, or have not, been taken with them. We have formerly published typical examples of such instances. As we shall presently see, this shows us why many cases of climatic and house asthmas have the same clinical aspects and etiology, and that all house asthmas occurring in places where the conditions lead us to suspect an asthmogenic climate (maritime, low, and damp localities in general) may be a true climatic asthma; though the onset is brought about solely by the contact with dust or infected furniture.

In regard to etiology, it is necessary to distinguish: (1) asthmas in which climatic influence alone is perceptible, devoid of all other allergens (true climatic asthmas), and (2) asthmas not specifically influenced by changes of locality, in whose pathogeny one perceives the intervention of numerous other factors (pollen, bacteria, etc.). We believe the latter cases to be invariably sensitive to active elements suspended in the air, principally fungi, although we cannot conclusively affirm this.

The probability of fungi acting as allergens has, as we have already mentioned, been shown by Van Leeuwen and his school, and confirmed later by other workers.

Cadham[10] in 1924 published an article proving that asthma in a series of workers in cornfields was due to wheat rust *(Puccinia graminis)*. Hansen in 1928 published a series of very interesting notes on asthma produced by sensitivity to fungi (aspergillus, glaucus, nidularis, *Penicillium glaucum*), and showed sensitivity to progressive dilutions by intradermal reactions. In 1929 we published several notes on asthma due to fungi, and laid great stress upon this etiology, not only in the case of climatic asthmas but in those of dwellings and in occupational asthmas (above all, flour dealers, or millers, and stores). Müller-Deham and Lasch[13] also investigated sensitivity to fungi in old asthmatic patients. Hopkins, Benham, and Kesten[14] in 1930 published a curious and well-studied observation on asthmatic patients sensitive to alternaria; and lastly Bernton[15] recently published a history of one patient sensitive to aspergillus, having discovered no other case among 125 investigated.

To begin with, we proceeded to study the abundance of fungi, and their filtration from air in Madrid and in the provinces of Segovia, Guadalajara, Zaragoza, Barcelona, the Levant coast (Sitges, Castellón, Valencia), and from the south (Huelva). Our object was to discover the ease of cultivation and the various species appearing in each locality. We employed Sabouraud's plates, momentarily opened outdoors and carefully closed immediately after. Seaside places and one or two damp inland towns (Zaragoza) gave the most abundant and early growth. The inspection of plates revealed that fungus was the same in one place

as in another with few exceptions. Three principal kinds invariably prevail: mucor, penicillium, and aspergillus. Different varieties might be recorded. Among the mucor, mucedo dominates; among penicillium, glaucus, crustacean and herbariarum species; in aspergillus, niger and fumigatus, as well as other kinds which we have not recorded, owing to the difficulty in doing so at the moment, and because we considered it unnecessary. Other forms (clamidoes, alternaria, etc.) proved much less abundant, and although we think a more systematic study and a more thorough record are necessary, such as have been made in pollen determinations, we have not as yet more exact data.

In dermal reactions we first employed prepared extracts from growth on Sabouraud's medium, subculturing the fungus in question and making skin tests both with pure cultures and with a mixture of various growths. For control tests we employed sterile medium, as its peptone content produced positive reactions in non-sensitive individuals. Later we resorted to the use of potato medium, which excels in growing aspergillus and penicillium. The potato becomes almost wholly invaded by the fungus, which grows rapidly, and the extract prepared from it is very concentrated. Since dermal reactions are not so reliable, we always made the intradermal test, and found no danger attached to it. We have also tried extracts obtained from cultures of plates exposed to the air without separating the individual fungi. We also tested with extracts from several kinds of mucor, penicillium, aspergillus, and alternaria cultivations.

We were able to show[4] that the cause of sensitivity to dust in dwellings is in some cases actually a sensitivity to fungi existing in dust. In addition we have had 14 strongly positive fungus reactions among 17 cases of exclusively climatic asthma. *The proof that we were dealing with a real sensitivity was indicated by passive transfer (Prausnitz-Küstner's method) which was tried and obtained in three cases.* Van Leeuwen[1] and Hansen[11] also succeeded in obtaining passive transfer to fungi. *A provocative test wherein symptoms developed on exposure was likewise successful.*

Probably the most demonstrative of our early cases was that of a patient, a native of Almería, who was examined by us previous to our study of the rôle of fungi in climatic asthmas. She suffered from very acute attacks, which were at first usually nocturnal but later on became prolonged in the form of a true asthmatic crisis, lasting several days. The attacks disappeared after she left home on her way to us in Madrid, and it is interesting that they did not reappear while she was in Granada. Feeling convinced that we were dealing with a case of climatic sensitivity, although we had not obtained positive skin reaction, we suggested that she should remain in Madrid, where she found work. In December, 1929, she returned home to see her people but was attacked by asthma at the last station just before Almería, and remained in a con-

stant state of dyspnea all the time she was at home. Feeling convinced, as we had already told her, that the dyspnea would never leave her while she remained in that locality, she left the place while having a severe attack which continued until she was 15 kilometers from the town. She arrived in Madrid perfectly well and has not suffered from an attack since. She reacted positively to a mixed culture of maritime air and was negative to all others. We also made several tests with different fungi and obtained a strongly positive reaction with *Penicillium glaucum*. Serum was taken from the patient, and passive transfer to this fungus was applied to a nonallergic person. A strongly positive reaction occurred. With a view to acquiring more convincing proof of the etiology of the patient's symptoms, a culture of penicillium was sprayed (without her knowledge) on her pillow. Although she had been a whole month in the clinic without a single attack, yet that night she had a very bad one. Throughout the following day she was perfectly well, and the following night she suffered again an even more intense spasm. Then her pillow was changed and the attacks disappeared. We then commenced a mild treatment of desensitization.* The first injections were well tolerated, but from the fourth the patient suffered a slight attack which recurred after each new injection, until finally the attacks became constant, and she relapsed into a true asthmatic state. This did not disappear even with the cessation of injections. This condition lasted over a month, after which it passed, and at present she is living in Madrid in perfect health.

Perhaps one may ask, since the same fungi thrive in maritime and inland districts, why is it that climatic asthmatics only suffer from attacks in the former places? This is indeed a point which at first seems surprising, and our only explanation lies in the belief that the nature of the soil and the conditions of temperature and humidity favor more extensive reproduction of fungi in materials, wools, furniture, bedding, dust, etc., in the seaside localities. According to this theory, then, even in climatic asthmas the chief focus of sensitivity lies in dwellings, although the same allergen may exist in all houses in a similar climate, and symptoms may occur which show that atmosphere is not the direct vector of allergens.

Favoring this theory we can estimate the therapeutic value, at times decisive, of de-allergenation of the infected dwelling.

Tiefensee[16] has made a study of the distribution of bronchial asthma in Prussia with relation to geologic formations. Since in that country tertiary systems have no importance, he examined glacial and diluvial formations and noted that cases of asthma are plentiful only in places of interior moraines (districts of clay and marl soils with striated pebbles), deep alluvial valleys, and glacial troughs; while in sandy formations with abundant lateral and frontal moraines they are very scarce.

*The extracts are prepared at the Protos Institute under our direction.

In all probability the influence of geologic formations is an indirect one, especially as these vary in flora (plants and fungi) and all essential climatic factors.

A fact that at times obscures the diagnosis of the cause of an attack is that secondary sensitivities may be united with the principal or primary sensitivity. On occasions the problem appears still more complicated when we consider that as the allergenic state diminishes, the rapidity with which the individual responds may be drastically altered; and thus nonspecifically paroxysms may occur from causes other than hypersensitiveness. In the first place, phenomena of "conditioned reflexes" may determine the nonspecific influences, particularly if we think of the psychic individuality of the asthmatic, Reichmann,[17] Hansen,[18] Pollnow, Petow, and Wittkower,[19] Römer and Kleemann,[20] and ourselves.[4] In this way an asthmatic who usually suffers from attacks in damp climates may feel the bad effects of humidity in places where allergens are nonexistent. This also explains why roadside dust may cause the onset of an attack in patients who are susceptible to dust in their homes. However, we have observed that inhalation of house dust provoked Widal's hemoclastic crisis, whereas inhalation of roadside dust did not. Moreover, we obtained a positive intradermal reaction from the former and not from the latter.

Bahnung phenomena, or facilitation of reflex by force of reiteration of the same paroxysm, are also of importance here. Asthmatics with repeated attacks acquire the Bahnung from the attack, which might later be produced by other circumstances. This we believe to be true in many cases of so-called physical allergy (Duke[21]), in agreement with the suggestion of allergy to cold first made by Widal, Abrami, and Lermoyez,[22] and in other notes previously published by us.[23] Changes of temperature, humidity, etc., no doubt largely govern the asthmogenic effect of certain climates. The situation of the town in which an asthmatic lives, who finds himself worse while there, has some influence on the progress of asthma through meteorologic action in the same sense that is advocated by Mouriquaud and Charpentier[24] and de Rudder.[25]

Possibly the influence of certain climates may be explained by their special meteorologic conditions.

In other cases, one observes an apparent climatic influence, which is in reality very indirect. For example, the beneficial action of certain climates on patients suffering from pollen asthma is due to nonexistence of the specific plants in those places. Likewise at higher altitudes there is less pollen in the air, and finally, in rainy or foggy places pollen distributes itself with difficulty. This accounts for the frequency of asthma in some climates of northern Spain, but far from the sea, as for instance in the interior of the province of Santander. There owing to the existence of infected haylofts in the houses, as we ourselves have seen, asthmatics on leaving immediately recover.

Other instances of asthma occur in patients only at home, as in the case of a patient sensitive to feathers, wherein it was found that pigeon houses were numerous where he lived. Another patient of ours, sensitive to flour, had attacks in her village because opposite her house was a flour mill. The attacks disappeared when she was in Madrid.

In all these cases, however, the apparent effect of climate is more connected with the dwelling or the habitual place of residence.

Evident climatic influence will also be noticed in the extensive group of asthmatics sensitive to bacteria (bronchitic asthma), with which we treat in another study. The cause is an equally indirect one, conditions of cold and dampness favoring repeated attacks of true bronchitis, in which the asthmatic reaction appears.

CONCLUSIONS

1. Climate strongly influences the appearance of attacks in a very high percentage of asthmatics. Sometimes it does this through various nonspecific influences. At other times the existence of true allergens peculiar to climate is the direct cause of attacks.

2. Climate has an indirect influence on asthmatics sensitive to pollen or other allergens which exist more exclusively in the patient's locality. Also house asthma is not always climatic asthma but is occasionally due to some accidental factor, such as animals, corn, barns, haylofts, etc.

3. Climate may directly influence attacks in patients sensitive to allergens, but in which the chief factors are dampness, temperature, and meteorologic disturbances which can actually vary the rapidity of response, or act as a nonspecific excitant of the Bahnung brought about by repetition of attacks. The most frequent example lies in bronchitic asthmas (bacterial), where the accentuating influence of climate on bronchitis is nearly always very apparent.

4. True cases of climatic asthma in Spain are nearly always coastal, and are due to the existence of abundant fungi in the air and in household articles in those places.

5. Studies of the etiologic rôle of fungi are reported. Those principally responsible for attacks are aspergillus, mucor, penicillium, and, to a lesser degree, certain clamidoes. The present studies consider their cultivation from the air, specific skin tests, passive transfer, provocation of attacks by introduction of fungi in the patient's environment, and the demonstration of the hemoclastic reaction.

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DERMATITIS VENENATA DUE TO CHRYSANTHEMUMS*

Report of a Case in a Florist

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OCCUPATIONAL dermatitis is not an uncommon disturbance, and the recent use of the patch test has proved the relationship of the irritants used by the patient to the lesions. Among florists, skin rashes from the handling of various flowers, bulbs, etc., have been recognized. Primrose dermatitis is an outstanding example. Evidence is appearing that chrysanthemums may be a cause. A case was recently reported by Goldstein.[1] Nightingale about the same time described a case[2] in a market gardener with lesions on the extremities and face, in the form of a dry scaly, papular erythema. He found records of two other cases (1924, 1926) in the dermatologic department of the London Hospital and quotes Dawson (1908) and Kren (1927) as reporting one case each.

The following case is added to emphasize that these flowers probably are not an uncommon cause when lesions in florists are properly investigated.

R. N., florist, aged fifty years. For five successive years the patient has noted the appearance of the skin trouble on face, neck and wrists, beginning in the fall (September) and gradually disappearing in the winter (February). The attacks during the past two years (1930 and 1931) seemed to be milder. Twenty years previously he recalled a skin rash in the summer attributed to poison ivy. Our first observation of the patient was in 1930, when he presented himself with a dermatitis of the squamous type involving the face and neck. The skin was deep red, thickened, and the surface layer was dry and exfoliating. The wrists presented small papular lesions of varying age on a brawny purplish skin. Itching was marked. The hands, legs and body were free from lesions. At that time the patient was referred to me by the family physician for protein tests. Scratch tests for protein sensitization were performed with pollens, epidermals, and foods with uniformly negative results. The patient felt that his occupation was responsible and ventured that his skin eruption coincided with the arrival and disappearance of chrysanthemum blooms. He returned again in the fall of 1931 with a recurrence of the lesions in the same locations. General physical examination revealed no abnormalities; urine and blood counts were normal; Wassermann and Kahn tests on the blood were negative. The lesions were limited to the face and neck and the flexor surface of the right wrist. The lesion on the wrist was described

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by the patient as the only exposed skin surface besides the hands that came in direct contact with the leaves in the handling of the flowers.

As the dermatitis appeared shortly after the arrival of the smaller chrysanthemums (pompons), these were thought to be the most probable cause. The flowers are small, and the leaves often have a greasy surface. The pollen of the flower, the petals, and the leaves were dried and pulverized separately. Patch or contact tests were made on the flexor surface of forearm by applying the pulverized material separately on the intact skin, covering with waxed paper and sealing the periphery of the paper to the skin by means of adhesive plaster. In twenty-four hours irritation was noted. At the end of four days the arms were examined. The leaves caused a fresh, vivid, red erythematous lesion with small papules corresponding in appearance with the lesion on the wrist. The pollen gave a slight papular lesion with very slight erythema. The petals of the flower showed no evidence of irritation. Contact tests made with the pulverized leaves of the large chrysanthemums (show type) gave negative results. The leaves of this large type of chrysanthemum as a rule do not have the oily surface observed in the smaller forms. The small chrysanthemum (*Chrysanthemum indicum*) is the parent flower and has a small leaf with a distinctly oily and fuzzy surface and at times a slightly disagreeable odor. The large chrysanthemum is a variety obtained by cutting; its leaves are smooth and odorless. The irritant is apparently absent or markedly reduced in quantity in the large flower.

Two extracts were prepared from the leaves and stems of the small chrysanthemums (pompons). One was an ether extract and the other a watery extract of the residue after ether extraction. Coca's solution was employed as extracting fluid for four days. The ether extract after evaporation consisted of a deep green greaselike material. This was applied to the skin of the patient on one forearm, and the watery extract was soaked in filter paper and applied on the opposite arm. Both were covered as in the previous test. In twenty-four hours marked irritation was noted from the ether fraction. Examination on the fourth day revealed a marked lesion by this fraction and no reaction from the watery solution. Pyrethrum by scratch and patch tests gave no reaction; intradermal injection of the aqueous extract of leaves of chrysanthemums was negative.

Dr. Wm. H. Welker of the Department of Physiological Chemistry then prepared purer fractions of the leaves. These were tested in a similar way on the patient. At this time, however, the aqueous fraction was applied on the scarified skin on the possibility that the water soluble proteins might require an injured skin to produce reaction. The results, however, were negative with this aqueous fraction. The semiliquid portion of the ether extract, on being evaporated, formed material on the sides of the dish which had the physical properties

of typical fat. This fraction and the 95 per cent alcoholic extract of the remainder of the residue from the ether extraction gave marked reactions in forty-eight hours. The residue insoluble in the 95 per cent alcohol and readily dissolved in ether gave a slight positive reaction. These experiments indicate that the ether and alcohol soluble substances are responsible for reactions and that the water soluble proteins are not the cause. Lipoproteins, however, may be present in the ether fraction, and therefore protein sensitiveness cannot as yet be excluded. Further investigation is being carried out to determine the chemical nature of the irritant.

The fat fraction and the ether soluble fraction in patch tests on three normal persons and another patient with marked dermatitis of unknown origin gave negative results. Passive transfer was tried by the injection of 1 c.c. of patient's serum intradermally in the forearm of a normal person, and applying the fat portion the following day. Daily examinations for six days revealed no reaction.

Nightingale[2] made patch tests with the leaf on the back of his patient and obtained a dermatitis conforming to the shape of the leaf. From the size of the leaf it is apparent that the small parent type of chrysanthemum was used in the test. The lower surface of the leaf gave a marked vesicular lesion. Contrary to the experience in our case he obtained a local erythema but no vesicles from the petals. He painted three extracts of the leaves on the skin. The alcoholic and saline extracts gave no reaction and the ether extract produced only a slight erythema. In our tests, however, the ether extract gave the most violent reaction; the portion obtained by treating the residue from the ether extraction with 95 per cent alcohol likewise gave a marked reaction.

Pyrethrum causes a dermatitis of various types in insect powder factories. This powder is obtained from petals of the flowers of certain chrysanthemums. McCrod and his associates[3] believe that the dermatitis is caused by neutral ethers and certain acids. In patch tests on our patient pyrethrum gave no reaction.

Of the irritants causing dermatitis venenata the recent report of two cases due to application of wool fat in therapeutic ointments indicates the importance of some ingredient in fat as the active irritant.[4] The lipoid fraction of the pollen of ragweed in pollen dermatitis has been determined as the active irritants in patch tests.[5] In his work Huber[6] obtained positive tests with the ether extract of the leaves of burweed marsh elder in two patients with dermatitis. It is of interest that the irritant in rhus dermatitis (poison ivy) is described as an unsaturated compound of the aromatic series, soluble in ether or alcohol.[7]

SUMMARY

A case of dermatitis venenata is reported due to chrysanthemums (pompons). The leaves were largely the irritating factors. By patch

test the ether soluble fraction of the leaves gave positive reactions. The water soluble fraction containing most of the protein gave no reaction. Passive transfer was unsuccessful.

Dermatitis venenata due to chrysanthemums is an example of marked skin sensitiveness, such as is observed in rhus and primrose dermatitis.

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TREATMENT OF PHYSICAL ALLERGY

Treatment of Heat and Effort Sensitiveness and Cold Sensitiveness and Treatment of Contact Urticaria Caused by Light, Cold, and Scratches

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IN PREVIOUS papers, I described a condition termed physical allergy,[1] which resembles allergy caused by sensitiveness to material substances such as egg or pollen except for the fact that the reaction is caused specifically, and often only by the effect, of physical agents such as light, heat, cold or mechanical irritation or by the effect of heat generated by mental or physical effort. The term "physical allergy" was introduced and used in a noncommital way to mean nothing more than an analysis of the words would indicate, that is, "altered reactability to the effect of physical agents."

Two types of physical allergy were alluded to. The contact type in which reaction is confined to the area directly affected by the physical agent and the reflex-like type in which reaction occurs not only at the site of contact but in distant structures as well or in distant structures only. The former or contact type because of nontransferability is more closely related, I now believe, to the drug allergies than it is to pollen atopy; the latter, or reflex-like type, is due, I still believe, to a disorder in the mechanism which regulates body temperature.

Both types of illness may minutely resemble the allergies caused by material things, such as pollen or egg, and therefore have to be taken into account by physicians who treat hay fever, asthma and allied manifestations of allergy. Furthermore, in the treatment of physical allergy the same general principles of therapy can be used which prove effective in the treatment of other allergies, namely, avoidance of primary causes of illness, treatment of associated illness, specific therapy with the causative agents, nonspecific therapy and symptomatic treatment.

It is for the purpose of discussing the practical therapy of these conditions that the present paper is written.

CONTACT ALLERGY CAUSED BY LIGHT, COLD, OR SCRATCHES

Contact reactions caused by light or cold or mechanical irritation can effect mucous membranes as well as the skin. In fact in the case of high grade sensitiveness to light, visual disturbance follows exposure of the eyes to light, and in the case of sensitiveness to cold reaction in the mouth, esophagus and stomach follows ingestion of cold drinks. This suggests, therefore, that tissues beneath the surface can react if they are adequately exposed to the offending agent. Contact reactions when immediate and marked give rise to typical urticarial lesions. When re-

actions are delayed, dermatitis is the typical lesion and follows only the more prolonged exposures. Treatment of either lesion can be carried out along the same general lines but must be modified to suit the individual case.

Light Sensitiveness.—The treatment of patients who are highly sensitive to light demands adequate protection from exposure to light. Accidental exposure of large areas of skin may be followed by shock which may require the hasty use of adrenalin. Undue exposure of the retina to light may produce temporary blindness. Prolonged exposure of the skin to light can cause local destructive lesions, even necrosis. Repeated small exposures may cause organic changes in the skin, such as proliferative lesions, ulceration, scarring and also small discrete areas of locally increased sensitiveness which result in local urticarial reactions under the influence of very much smaller exposures to light. The skin areas between these lesions may have increased tolerance for light. In fact given areas of skin treated systematically with light may show markedly increased local tolerance for light and in addition localized areas of increased sensitiveness, also increased tolerance of untreated areas of skin.

Patients who are highly sensitive can avoid exposure to light which is beyond their threshold by staying indoors on sunny days and by wearing black clothing or colored clothing (except blue) when out doors on cloudy days. They get along better in damp climates because of the fact that violet rays of light do not easily penetrate air moisture.

Tolerance for light can be developed through systematically increased exposures of increasingly large skin areas of the body to sunlight or to artificial light containing the rays which affect the patient. Daily exposures should be pushed to the point of causing slight reaction or stopped just short of this. Skin areas should not be so large as to cause serious constitutional reaction. It would seem unadvisable to start with exposure of more than one-eighth of the entire skin area. This can be rapidly increased, however.

Patients who are sensitive to both heat and light should be treated with heat from a 15000 watt nitrogen lamp rather than from an infrared element—this to be followed by treatment with ultraviolet light. It is possible in many cases to develop practical tolerance, that is a degree of tolerance which is useful to the patient. In one highly sensitive case treated by Dr. Forster of Colorado Springs, tolerance was developed to such a degree that the patient could lie uncovered in the sunlight for hours. Tolerance in cases of this sort is due partly to increased pigmentation. If tolerance cannot be developed to a degree which is practically useful to the patient, it may be necessary for him to change his habits, occupation, mode of dress and climate so as to afford himself adequate protection from light.

Symptoms of generalized shock which follow overexposure of large areas of skin can be reduced by the use of adrenalin. The effect of

adrenalin is not grossly different from that to be obtained by adrenalin in the treatment of contact allergies due to egg or pollen.

Cold Sensitiveness.—Patients who are highly sensitive to cold must avoid exposure of large areas of skin to cold and must avoid situations and occupations which subject them to unavoidable exposure. Exposure to a moist wind between 5 and 15 degrees Centigrade or a bath at that temperature can produce severe generalized shock in certain individuals. Individuals of this sort can live in safety and comfort in warm climates or in cold climates if they can stay indoors when the outside temperature is low. Cold drinks and cold foods must also be avoided.

Relative tolerance can be obtained in cold sensitive cases through application of cold water or ice rubs to gradually increasing areas of skin surface. Increased tolerance can be obtained usually within a period of two weeks.

Adrenalin subcutaneously relieves cases manifesting evidence of shock following accidental exposure of large areas of skin to cold.

Scratch Sensitiveness.—This illness may be very disagreeable. Several of my most sensitive patients were rendered miserable by itching urticaria whenever they were subjected to unusual rubbing of the skin by rough garments or from slight scratches made involuntarily. Patients of this sort are occasionally so sensitive that the eruption actually appears to occur almost spontaneously. These may be rendered relatively tolerant by frequent brushings of the skin with a stiff brush—in fact, in almost every case treated in this way improvement can be expected. The symptom, itching, is almost completely relieved in a majority of cases within a few days, and the urticarial reaction and erythemia are reduced in their intensity.

HEAT AND EFFORT SENSITIVENESS AND COLD SENSITIVENESS, REFLEX-LIKE REACTIONS

Reflex-like reactions, that is, reactions which occur not only at the point of contact with the offending physical agent but also in distant structures or in distant structures only, are caused in the gross majority of cases by an exaggerated or perverted response to the effect of heat and effort or to the effect of cold. The former type of sensitiveness is much the more common. The more common manifestations are: prostration such as those commonly diagnosed heat prostration, effort syndrome, or fainting; allergic reactions similar to those caused by sensitiveness to food or pollen such, for example, as asthma, urticaria, dermatoses, noninfectious coryza, gastrointestinal reactions; neurologic reactions such as tremor, weakness, headache or even convulsions, and finally shock symptoms such as collapse, elevation of pulse rate, lowered blood pressure, disappearance of pulse and respiration and cyanosis. The reactions may resemble true allergy even in the occurrence of delayed reaction and in the occurrence of reactions which follow prolonged repeated contact. The pathogenesis of this condition has been discussed in detail in a

previous paper and need not be repeated here. It is believed to be due directly to a gross defect in the heat regulating mechanism caused frequently by a febrile disease and in older individuals often by organic diseases which interfere with the effectiveness of the mechanisms which regulate body temperature.

Heat and Effort Sensitiveness.—Sensitiveness to heat and sensitiveness to effort can occur separately, although as a rule if one is present the other can be demonstrated in slight or marked degree. The condition is characterized by a syndrome of symptoms such as those above enumerated which consistently follow the heating up of a patient beyond his threshold of tolerance. The effect appears to be the same whether heating occurs as a result of contact with warm or hot air, water or hot objects or through a reduction of heat loss caused by moisture in the air or through the heating effect of effort. The reaction can occur as a result of the overheating of the blood or of a given organ, or as a reaction to the sense of heat.

Pathologic responses to heat in the gross majority of cases seem a reaction to the sense of heat rather than to a rise in blood temperature and in cases of this sort typical symptoms of which the patient complains can be reproduced by the heating of an extremity distal to the site of application of a tourniquet which stops the return flow of blood from the extremity. A similar reaction can be produced as a general rule through the effect of effort and in highly sensitive cases through the effect of so little effort as the raising up out of a chair, of sitting up in bed, or raising the arms above the head two or three times. A reaction so produced can be stopped or prevented almost always by the simultaneous application of cold to the skin even distal to a tourniquet which stops the return flow of blood.

Patients of this sort are tormented by the effect of heat and moist air and instinctively choose habits and occupation which do not subject them to overheating beyond their tolerance. They instinctively fear the effect of heat and effort and subconsciously avoid it. They choose a quiet life and on account of this give an impression of laziness. The fact is that patients of this sort may be extremely alert and would be active if their physical capabilities kept pace with their desires. It is unfortunate for the patient if necessity forces a change in habit, occupation or climate which he has instinctively chosen. In this case he is likely through overheating to be prostrated or pitched into severe attacks of asthma, allergic coryza, urticaria, dermatitis, headache or shock whenever he is forced into situations in which he becomes heated beyond his threshold. Patients of this type do much better in a dry climate whether warm or cold because of the easing effect of dry air upon the activity of the heat regulating mechanism. Dry air through promoting evaporation has a cooling effect not only on the skin but more important still upon the respiratory membranes.

Patients who are highly sensitive to heat are difficult to treat unless

the physician understands the condition and can give the patient what he needs. Tolerance for heat can be raised in a great many cases if the patient's reaction to heat is not too dreadful. If the reaction produced by heat is an inconsequential one, such as pruritis, nasal allergy, or asthma, the symptom produced by therapy can be tolerated until it is relieved by cold. However, if the reaction produced by heat therapy is a convulsion which is difficult to control with adrenalin, ice rubs or morphine, the patient cannot well be treated by the method to be described.

The average severe case requires the help of a nurse or some member of the family who can be taught to care for the patient and who can enforce treatment with heat, cold and effort. It is best in the beginning of treatment to raise tolerance for heat by applying the heat of a large nitrogen lamp (at least 1500 watt) to the skin from a distance of about 18 inches and continue the application to the point of starting a reaction, that is to the point of reproducing the symptom complained of by the patient. This should be immediately stopped or controlled by the rapid rubbing of the skin with ice. In patients who react within a matter of seconds or minutes, this method of treatment can be carried out easily and within a period of an hour a number of reactions can be precipitated and relieved by the alternate application of heat and ice. Tolerance for heat can be raised appreciably in this way within a week or so in a majority of cases, and coincident with this, one can almost always note an appreciable improvement in the patient's illness. In several of my cases a few weeks' treatment raised tolerance from a point where a five-second exposure to heat would cause reaction to a point where a thirty-minute exposure could be tolerated without apparent ill effect. This, as a rule, transforms an almost bedridden patient into an ambulant one.

After tolerance for heat has been increased in marked degree, tolerance for effort must be developed through subjecting the patient first to the effect of muscular effort and later to the effect of mental effort.

It must be borne in mind that the heat produced by effort exceeds the heat lost from the skin and respiratory tract unless a change in the vessels of the skin and bronchioles and unless a change in respiration rate compensate for it. Also it should be remembered that mental effort generates heat through increasing muscular tone and movement even though heat production in the brain itself might be small. A reaction precipitated by effort can be stopped as a rule by an ice rub. At first, the effort of sitting up in bed may precipitate reaction. Tolerance for effort can often be increased by systematic exercise from this point to a point where the patient can indulge in most of the activities required of him.

Patients who are sensitive to heat and effort as a rule have small flabby muscles even though they may be well nourished or even fat. This is due no doubt to the quiet life they are forced to lead and probably also to deficient muscular tone. Treatment with heat and forced effort

as described is associated in successfully treated cases with a rapid development of muscular tissue.

In the beginning of treatment excessively sensitive patients shun the effect of heat and effort as they would shun a visible poison. A great deal of persuasion has to be used to get them to exert themselves. In fact, at first it may require the combined efforts of the family, nurse and physician. However, confidence is gained as soon as the patient discovers that the effect of ice will immediately stop a truly distressing reaction caused by heat or effort. Fears and phobias commonly found in patients highly sensitive to heat and effort are founded on reality and usually disappear as soon as the patient learns to avoid overheating and learns quickly to relieve reactions when they occur.

Patients who are sensitive to the effect of mental as well as physical effort have to be treated finally through forced mental activities. At first by enforced reading, later playing games, watching athletic contests, attending theaters and study. After tolerance for physical effort is developed, tolerance for the effect of mental effort is relatively simple, and the result may be the transforming of a hopeless, useless, invalid into a good state of health.

Heat and effort sensitiveness can be relieved or benefitted very frequently by the treatment of other illnesses which contribute to the patient's discomfort. This is especially true of illness such as the allergic diseases which may cause the same illness as that caused by heat and effort. This is also especially true of other diseases, such as cardiac or renal disease, anemia and diseases of blood vessels, skin or lung which interfere with normal reactions which regulate body temperature. Treatment of illnesses such as these may reduce the severity of reaction to heat and effort. In a majority of severe cases, however, especially those which occur in younger individuals, no associated illnesses may be found. The patient may be physically and mentally normal except for perverted responses to the effect of heat and effort. The following case report shows a therapeutic result which can be obtained in the treatment of an apparently hopeless case of effort syndrome caused by sensitiveness to heat and effort.

TREATMENT OF A CASE OF EFFORT SYNDROME CAUSED BY HEAT AND EFFORT SENSITIVENESS

A young man, aged twenty-one years, following an attack of scarlet fever three and one-half years before, had been confined to his house because of weakness, tachycardia, and fainting spells. For two years he had been confined to his bed, using a bed pan because of weakness, exhaustion, and tachycardia which followed such slight effort as getting out of bed or even of sitting up.

Physical examination and laboratory tests and skin tests were negative.

The effort of getting out of bed and walking around the room, which was done with very apparent distress, caused a doubling of the pulse rate, a feeling of complete prostration, and tremor. Rubbing the patient with ice immediately reduced the pulse rate to normal and relieved the tremor and feeling of prostration. Application of heat from an ordinary electric heater for five seconds caused the pulse rate

to double and caused the tremor to appear. This was relieved within a matter of seconds by rubbing the arms with ice.

The patient was brought to the office in an ambulance and treated at daily intervals with frequent alternations of heat and ice. Tolerance was developed from a point where he could scarcely stand a five-second exposure to the heat of a nitrogen lamp to such a point that he could tolerate, without ill effect, as much as a half hour's exposure. Tolerance for effort was gained through graduated exercise to such a point that he finally, after six months, could engage in wrestling bouts without ill effect. This was associated with a gain in weight of 23 pounds and marked development of muscles. Tolerance for mental effort was rapidly developed through forced attendence to school, theaters and other public places which he instinctively shunned. As soon as he discovered that he could stop an attack caused by mental activity through applications of ice or cold water to the hands and arms, the phobia which forced a secluded life vanished.

A relatively large proportion of cases react more markedly to the effect of heat and effort when body temperature is lowest so that the avoidance of high grade subnormality in temperature becomes important. Prolonged depression and inactivity or exposure to cold may intensify the reactions to heat and effort. On the other hand many patients are definitely benefitted through the effect of fever. A febrile disease almost always gives temporary relief and frequently prolonged relief. Fever can be given artificially through the subcutaneous or intravenous injection of Bacillus coli. Through the use of this in gradually increasing dosage for a period of one or several weeks and increased to the point of giving mild febrile reactions, I have been able to effect clinical relief in several desperately afflicted patients. The intravenous use of Bacillus coli is likely to give a quick febrile attack even if given in doses as small as 10,000. Although I have had no unfortunate results with this form of therapy, I think the subcutaneous use of Bacillus coli is much safer. I do not wish to recommend this arbitrary method of treatment strongly, but I can frankly say that I believe many of the therapeutic results that follow the use of autogenous vaccines, peptone and milk in the treatment of persons with noninfectious coryza, asthma, eczema and urticaria frequently owe their beneficial effect to the elevation of body temperature from subnormal toward normal or above normal rather than to some other specific effect of the therapy.

Temporary remedies that are useful for symptoms such as coryza, asthma, urticaria and pruritus are epinephrine, pituitrin, ephedrine, atropine and the salicylates. Morphine and alcohol may be effective. Morphine is rarely justified. Acids are indicated if achylia is found.

The fact is that indications for symptomatic remedies and the effect of symptomatic treatment are about the same for a patient with physical allergy as for patients with true allergy. For detailed discussion of this the reader is referred to previous communications.

Temporary symptomatic relief can often be obtained through the use of hot or cold baths given when the patient needs them. Cold baths for the temporary relief of an attack may be effective within a few moments

and may give a sensational result. Hot baths at midnight for the prevention of a drop in temperature from relatively normal to high grade subnormality may be effective in preventing early morning attacks.

Cold Sensitiveness.—Cold sensitive patients are much more fortunate than heat sensitive patients. In the first place, it is much easier to avoid overcooling than it is to avoid overheating. Also, if a person is chilled, he can so easily relieve himself through exercise.

The cold sensitive case is also more fortunate because of the fact that effort instead of causing illness usually gives relief. The very illness, therefore, frequently makes an energetic individual highly successful in the vocation which he chooses—in fact, cold sensitive individuals frequently choose a vocation which requires high grade activity for no other reason than the fact that it promotes a feeling of well-being. This accounts, I believe, for the activity of many individuals who keep themselves strenuously occupied and could account for a number of historical characters whose lives were typified by constant activity. It is unfortunate for such an individual if a change in circumstances forces him to lead a life of quiet. Such a change may be followed by complete break down in health.

Cold sensitive patients, like heat sensitive patients, tolerate temperature changes which are damaging to them better in a dry climate than in a moist climate. Dry air, whether hot or cold, is easier to tolerate than humid air.

Fortunately, patients can frequently gain tolerance for cold through the use of frequent cold baths. This is often a most useful remedy in a proved case of cold sensitiveness. Frequently, one can effect complete clinical relief in a cold sensitive patient through so simple a measure as having the patient take a cold bath each morning. A cold bath for fifteen to thirty seconds frequently repeated may suffice to give tolerance. Cold sensitive patients are frequently hyperesthetic to cold. In this case, they may shun exposure to cold during the early part of their treatment. After a time, they are likely to learn to enjoy exposure to cold. Frequently, patients tolerate a rapid rub with ice better than a cold bath. If the ice is moved rapidly enough over the skin, it does not cause a disagreeable sensation of cold. Ice should be applied over the entire body and the rub should be stopped short of producing shivering.

Nonspecific therapy should be used with care if at all in the treatment of cold sensitiveness. It appears possible through this agency to change cold sensitiveness to the less favorable condition, heat sensitiveness.

Symptomatic remedies suggested in the treatment of heat sensitive persons can be used to advantage in the treatment of cold sensitive patients.

SUMMARY AND CONCLUSIONS

In this paper I have discussed the treatment of illnesses described in previous papers under the term physical allergy and under the terms

heat and effort sensitiveness and cold sensitiveness and under the term urticaria caused by light, heat, cold, and scratches.

Symptoms which occur clinically as a result of the conditions grouped under these titles may be exactly like those caused by allergy in patients sensitive to egg, milk or pollen and include such illnesses as asthma, coryza, urticaria, angioneuredema, dermatoses or may be similar to illness grouped under the term vagotonia including so-called vagal crises in the gastrointestinal and urologic tract or may be identical to certain neurologic symptoms caused by organic illnesses, such as headaches, convulsions, prostration, and finally they may be associated with hypersusceptibility to infection, especially infections in the respiratory tract and skin.

I have studied the effect of treatment in these so-called physical allergies (altered reactibility to the effect of physical agents) now for a period of fifteen years and have worked out treatment methods which are reasonably successful in a majority of cases and brilliantly successful in selected cases.

If the agents responsible for reaction can be either avoided or administered to the patient in ascending doses in such a way as to give practical tolerance, the result is likely to be brilliantly successful.

The recognition of the conditions referred to in this paper is important and should not be neglected by careful physicians. The afflicted patients drift to physicians in almost every line of practice, and unless their cases are correctly diagnosed and correctly treated they are destined to remain invalids or semi-invalids who receive little sympathy from any one.

Symptomatic treatment with heat or cold as indicated may be a life-saving measure in the case of profound reaction.

Fears and phobias based upon a subconscious realization of a weakness may disappear overnight when the patient learns to avoid exposures and situations which subject him to exposures which precipitate attacks. He gains confidence also when he learns how quickly to relieve attacks which are not only disagreeable and embarrassing, but actually dangerous.

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Society Proceedings

THE CHICAGO SOCIETY OF ALLERGY

MEETING OF MARCH 21, 1932

Studies in Tissue Immunity.* PAUL R. CANNON, M.D. (Abstract.)

The cutaneous allergic reactions obtained in animals hypersensitive to antigenic substances have not been studied sufficiently from a morphologic viewpoint, and their significance to the organism as a whole is too little considered. Opie has suggested that these cutaneous reactions are instances of anaphylactic inflammation and occur because of the union of antigen and antibody in the tissues. As the result of such a local union, inflammation ensues, the antigen is localized and in the process, generalization and the more serious consequences to vital organs are prevented. The injury to the tissues, then, is part of a defensive mechanism by which vital organs are protected at the expense of local injury.

We have studied several aspects of the problem by observing the inflammatory reaction in the skin of guinea pigs inoculated locally with a heat-killed staphylococcal vaccine and later infected with a living culture of the same strain. We have observed that such an infection, in animals previously inoculated locally, is a circumscribed lesion, which heals quickly; whereas, in normal animals, there is a diffuse cellulitis, frequently leading to death. Morphologic studies show that this localization in the locally immunized animal is due, principally, to the presence of histiocytes and leucocytes, which react more effectively against the staphylococci because the latter are opsonized and agglutinated, presumably by specific antibodies formed in situ.

In confirmation of the latter idea, skin tissues from rabbits repeatedly injected intracutaneously in a localized area with a formolized vaccine of *B. paratyphosum B,* have been extracted in a glycerol salt solution extractive and have been found to contain higher concentrations of agglutinin than comparable amounts of spleen, liver and blood serum similarly treated. Therefore it is apparent that the introduction of an appropriate antigen into an area of mobilized histiocytes may lead to the local formation of antibodies.

These findings tend to corroborate some of the views of Opie concerning anaphylactic inflammation; furthermore, they add evidence to the idea that local immunity may exist and be dependent upon the local concentration of phagocytes and antibodies.

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Allergy as a Factor in Ulcers of the Digestive Tract. Wm. L. Beecher. (Abstract.)

The author cited reports by himself and others as to the allergic origin of canker sores and argued that peptic and colonic ulcers might also be due to allergy. He believes allergic reactions, causing the Arthus phenomenon, herpetic eruptions, or urticarial lesions, produce a lessened resistance to digestive ferments, and that ferment action produces the actual ulcer. The persistence of the allergy prevents healing, and a recurrent allergic reaction accounts for seasonal incidence of ulcers.

Various etiologic theories were examined. Some were found to be inadequate and others best explained by allergy. References to articles by Jones, Isaacs, Held, Ivy and others were made in support of the allergic theory.

Allergy as a factor in digestive ulcer was claimed in only a portion of cases, and members of the society were urged to investigate further to prove or disprove this contention.

Errata

In the abstract of the article by Harry L. Huber, *A Dermatitis Due to the Burweed Marsh Elder,* page 316 of the March, 1932, issue, in the fourth and fifth lines "Twenty-four patch tests" should read "twenty-four hour patch tests." In the second to last line the word "burwood" should be "burweed."

Department of Reviews and Abstracts

Selected Abstracts

Congenital Protein Hypersensitiveness in Two Generations. Ratner, B., and Gruehl, H. L.: J. Exper. Med. **53**: 677, 1931.

The passive sensitization of a fetus in utero has been previously demonstrated. Such sensitization is brought about by the transmission of antibodies from the mother through the placenta and is of a duration of only two and one-half months or thereabouts. That the fetus can be actively sensitized in utero has recently been shown. Such sensitization is brought about by the transmission of soluble antigen from the mother through the placenta.

Experiments were undertaken to discover whether active sensitization so induced is transient or persistent. In demonstration, only such families could be used in which birth occurred within a few days after the original parenteral injection of the pregnant animal so that antibodies could not have been established in that animal. Records are given of 6 such families. Large female guinea pigs not previously treated were bred with males. The pregnant animals received massive parenteral doses (10 to 12 c.c.) of horse serum intravenously as near term as possible.

Results showed that when such injection occurred two to four days prior to parturition, the young were not sensitive at birth, but subsequently developed hypersensitiveness which was of considerable duration. The young could be thrown into lethal anaphylactic shock by injection of horse serum, or if permitted to mature and reproduce in their term, could passively sensitize the succeeding generation by the passage of antibodies through the placenta. Thus a female sensitized immediately before parturition could sensitize two succeeding generations.

Allergy to White of Egg in Infants. Woringer, P.: Compt. rend. Soc. de biol. **108**: 6, 1931.

A hypersensitiveness to egg white has frequently been noted among eczematous infants. Experiments by the author revealed the fact that 50 per cent of the infants with chronic eczema under his observation gave positive skin reactions to dilutions of egg white injected intradermally.

The origin of such hypersensitiveness, it was considered, might be explained by three possibilities:

1. Sensitization of the infant following the ingestion of egg white.
2. Sensitization of the infant during intrauterine life to egg white absorbed by the mother and passed by her into the fetal circulation.
3. Ovoalbumin allergy not an acquired function but an hereditary cellular property.

The first possibility was excluded by the fact that a certain proportion of the infants found sensitive to egg white had received nothing but cow's milk from birth.

Of sensitization to egg white in utero the author has found no convincing proof. The mere introduction of egg white into the circulation of an infant is insufficient to produce sensitization. In his experience, the author has never been able to sensitize a normal or eczematous infant with either small or large doses of egg white. It appears probable to the author, that in this respect the fetus behaves in similar manner to the infant.

The fact that allergy is so frequently a familial malady inclines the author to the belief that it is an hereditary cellular property and not an acquired function.

A Method of Evaluation of Ovoalbumin in the Serum of Subjects Allergic to Egg White. Woringer, P.: Compt. rend. Soc. de biol. **108**: 10, 1931.

The proposed method is based on the neutralization in vitro of antibodies by antigen with human skin as an indicator. A serum giving a positive Prausnitz-Küstner reaction is rendered inactive by the addition of a sufficient amount of egg white. If this serum is mixed in varying proportions with egg white, the mixtures with little egg white will give the reaction, while the mixtures with much of it will not give the reaction. The mixture which with the slightest quantity of antigen no longer gives the reaction is the one which approaches the nearest to neutralization of antigen and antibody. Mixtures of serum and egg white in dilutions of from 1:50 to 1:500,000 are prepared and put into ampules and used for the Prausnitz-Küstner reaction. If, for example, a reaction is obtained with dilution 1:200,000 and no reaction is obtained with dilution 1:100,000, then the value of the serum in antibodies is estimated as 1:100,000; i. e. to neutralize 1 c.c. of egg white, 100 liters of serum are necessary.

The Prausnitz and Küstner Test in Allergy to Egg White in Infants. Woringer, P.: Compt. rend. Soc. de biol. **108**: 8, 1931.

Trial was made of the Prausnitz-Küstner test in sixteen allergic infants. The results were positive 11 times and negative 5 times. The author concludes that the reaction when it is positive confirms the re-

sults of other tests, but when it is negative, does not nullify the results of other tests.

Further experiments with graduated doses of antigen tend to show that in the Prausnitz-Küstner reaction, it is the combination of the antigen and the antibody which exercises an irritating action upon the skin. The skin itself plays the rôle of revealer of a chemical or physicochemical process in which it does not participate.

Infective Asthma: Indication of Its Allergic Nature. Cooke, R. A.: Am. J. M. Sc. **183**: 309, 1932.

The question is raised whether or not asthma of infective origin should be considered as an allergic reaction. The problem is viewed from the angle of heredity and of eosinophile response.

Six hundred and eighty-eight cases of asthma, grouped according to cause as nonsensitive (infective), sensitive (atopic), and combined, were studied in relation to positive antecedent history. The rôle of heredity in sensitive asthma is well known. Results of the study showed a positive antecedent history in 52 per cent of the atopic cases, in 45 per cent of the infective, and 55 per cent of the combined. The indication is for an identity of the transmitted biologic factor in nonsensitive and sensitive asthmatics.

Eosinophilia has long been regarded as an allergic phenomenon. Experimentally, it is produced under conditions considered favorable to sensitization. A brief résumé is given of the various theories of the origin of the eosinophile cell and its function in normal and pathologic states. Its presence in asthma of the skin-sensitive type is noted. Study of 131 cases of asthma and allied disorders showed an eosinophilia, either local or general, to be as frequent in asthma of infective origin as in asthma of the skin-sensitive type.

The conclusion is drawn that asthma of an infective origin should be considered as an allergic reaction.

Sensitization Dermatoses of Nonfungous Nature. White, C., and Taub, S. J.: J. A. M. A. **98**: 524, 1932.

The observation is made that in certain cases an eruption of the glabrous skin of the body occurring immediately or a short time after a flare-up of a fungus infection may be due to sensitization to substances other than the circulating fungi or fungus toxins. The fungus is essentially only a predisposing factor inducing a hyperallergy.

Four case reports are given. In Case 1, the patient was first admitted to the clinic with an eruption on the foot which was diagnosed as a ringworm infection. Some months later she suffered an acute flare-up on the hands. There was an accompanying ringworm infection on the foot. The following year she appeared again with an acute flare-up on the hands and arms. This time there were no lesions on the feet. Skin

tests showed a strongly positive reaction to cottonseed oil. Elimination of this article from her regular diet produced a clinical cure. Prior to the original ringworm eruption, cottonseed oil had been eaten many times with no ill effects.

Case 2 presents an example of ringworm of the fingers and nails with a subsequent dermatitis due to a sensitivity to oatmeal.

Case 3 cites an example of fungus infection of the root with a secondary eruption on the hands, forearms, and thighs traceable to a sensitivity to buckwheat. Prior to the fungus infection, buckwheat had been eaten with impunity.

In Case 4 the original infection was on the scalp. A subsequent eruption on the face was traced to a sensitivity to silk.

The conclusion is drawn that in some people with fungus infections, the skin is so altered that it becomes sensitive to certain foods and other irritants to which no clinical symptoms had previously appeared.

Research on Asthma. London Correspondent: J. A. M. A. **98**: 241, 1932.

A further report of the progress of the Asthma Research Council takes into special consideration the "urinary proteose" mentioned in previous reports. This proteose is excreted in the urine by patients during an asthmatic paroxysm. One patient usually does not react to the proteose of another, but in cases of specific sensitization, such as horse asthma, one case of horse asthma will react to the proteose from another case. Large doses of the proteose induce an asthmatic attack, but small doses often desensitize the patient and give relief.

Research is also being done in the bacteriology of the sputum. It has been found that many asthmatics excrete in the sputum an organism that has the property of forming histamine both in the bronchial secretions and in vitro on culture mediums. The problem is being studied of the nature of these bacteria, their seasonal variation, and the possibility of their inducing asthma by the local formation of histamine in the lungs.